Comparison of the Likelihood Ratio and Identity-by-State Scoring Methods for Analyzing Sib-Pair Test Cases: A Study Using Computer Simulation

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AOKI, Y., NAKAYAMA, Y., SAIGUSA, K., NATA, M. and HASHIYADA, M. *Comparison of the Likelihood Ratio and Identity-by-State Scoring Methods for Analyzing Sib-Pair Test Cases: A Study Using Computer Simulation.* Tohoku J. Exp. Med., 2001, **194** (4), 241–250 — To assess the power and significance of the likelihood ratio (LR) and the identity-by-state scoring (IBS) methods for a pair of siblings, we performed computer simulations by use of 10 DNA markers (HLA-DQ α , D1S80, and 8 short tandem repeat loci) that were frequently analyzed in paternity tests in Japan. The combined power of discrimination of these 10 markers in the Japanese population is 0.999 999 999 98. Pedigrees each consisting of 10 000 pair of full-siblings, half-siblings and unrelated individuals were generated and typed on all markers as random samples. Both the summation of $\log_{10} LR$ and IBS of each group had approximate standard normal distribution with significant differences between the means. Statistical studies showed that the LR method has 91% power to detect unrelated individuals and 38% power to detect half-siblings as not full-siblings with a 5% false-positive rate, whereas the IBS method does 87% and 42% powers, respectively. In 62% of full-siblings, in contrast with only 0.2% of unrelated individuals, the values of LR exceeded 100 which was equivalent to 0.99 of probability of full-sibship at 50% prior probability. The advantage of the LR method over IBS method was convincing especially for the detection of unrelated individuals as not half-siblings, however, the latter would be also informative for sib-pair tests if sufficient number of polymorphic markers are available. ——— genetic markers; likelihood functions; computer simulation; sibling; probability

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Received April 24, 2001; revision accepted for publication August 25, 2001.

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Some algorithms have been proposed to calculate or evaluate probability of sibship in the cases lacking parental-genotype information. For forensic purpose, likelihood based method has been widely accepted (Brenner 1997). The likelihood ratio (LR) for full- and half-siblings can be calculated by generalizing hypothesis in the paternity cases. On the other hand, identity-by-state (IBS) scoring method, which were based on summation of the number of alleles shared by the siblings, were recently applied to detect pedigree errors (Ehm and Wagner 1998). This method is one of the approaches to analyze the data of affected sib-pair tests which are used extensively for mapping or linkage analyses in the field of genetics (Lange 1986; Thomson 1986; Bishop and Williamson 1990).

Sib-pair relationships can not be excluded by the typing of the simple diallelic genetic marker systems, and it is hard to draw definite conclusions compared to the paternity trio cases. Recent DNA technology, however, would push through the impasse because of its high polymorphism. DNA analyses of alleged siblings are now often performed as forensic service. Whereas, the detection of pedigree errors can be essential for genetic mapping project. Errors will often inflate distances in genetic maps and reduce the power to locate disease genes (Ehm and Wagner 1998). The aim of this study is to discuss and compare the power and significance of two methods; LR and IBS methods for sib-pair test using some single locus DNA markers.

MATERIALS AND METHODS

DNA markers

Ten DNA loci with relatively large database on allele-frequency distribution among the Japanese population, D1S80, HLADQ α , CSF1PO, TH01, TPOX, vWA, D5S818, D13S317, D7S820 and D16S539, were employed for analyses. Allele distribution at D1S80 and HLADQ α were reported by Technical working

group on forensic DNA typing method (1994). The population data of the other 8 short tandem repeat (STR) loci were based on the summation of those of Japanese populations reported previously (Fujita et al. 1995; Dewa et al. 1996; Fujii et al. 1996; Nagai et al. 1996, 1998; Nakamura et al. 1996; Nata et al. 1996; Takahashi et al. 1996; Tamura et al. 1996; Uchimura et al. 1996; Yamaguchi et al. 1996; Wang et al. 1996; Kozma et al. 1997; Technical working group on forensic DNA typing method 1997; Takayanagi et al. 1998; Yamamoto et al. 1998; Yoshida et al. 1998) and typed in our laboratories ($n=933-3516$). No significant differences on allele frequency distribution were observed among these reported data and ours by chi-square analyses. The loci are considered to be on distinct chromosomes and also in linkage equilibrium. Therefore, they can be sorted by Mendel's laws, and the results for each locus can simply be multiplied or summed. Accumulated power of discrimination of the 10 markers is 0.999 999 999 98 (Grunbaum et al. 1978).

LR method

LR is the ratio of two probabilities of the same event under different hypotheses. In this study, probability of the combination of two genotypes for full-sibship, half-sibship, and unrelated individuals were calculated by use of the population data. In brief, the genotypes of the parents of the two individuals were estimated with probability under the assumption that the two individuals shared two parents, one parent or none. Then the probability that the children of the parents with estimated genotypes had the combination of the genotypes of the two individuals was computed. If LR comparing full-sibship to half-sibship of a pair of individuals is t , the data are t times more probable if the individuals are full-siblings than if they are half-siblings (Table 1) (Brenner 1997).

Let

f_i : Conditional probability of the combina-

TABLE 1. *Conditional likelihood ratios of siblings of each combination*

	Genotypes of 2 individuals	Likelihood ratio (X/Y) comparing		
		Full to half- sibship	Half-sibship to unrelated	Full-sibship to unrelated
1	$PP \times PP$	$\frac{p+1}{2p}$	$\frac{p+1}{2p}$	$\frac{(p+1)^2}{4p^2}$
2	$PP \times QQ$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$
3	$PP \times PQ$	$\frac{p+1}{2p+1}$	$\frac{2p+1}{4p}$	$\frac{p+1}{4p}$
4	$PP \times QR$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$
5	$PQ \times PQ$	$\frac{2pq+p+q+1}{4pq+p+q}$	$\frac{4pq+p+q}{8pq}$	$\frac{2pq+p+q+1}{8pq}$
6	$PQ \times PR$	$\frac{2p+1}{4p+1}$	$\frac{4p+1}{8p}$	$\frac{2p+1}{8p}$
7	$PQ \times RS$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$

p, q : gene frequencies of alleles P and Q , respectively.

tion of the DNA profiles of the two individuals at locus i assuming they are full siblings

h_i : Conditional probability of the combination of the DNA profiles of the two individuals at locus i assuming they are half-siblings

u_i : Conditional probability of the combination of the DNA profiles of the two individuals at locus i assuming they are unrelated

Then

$\frac{f_i}{h_i}$: LR of the combination comparing full to half-sibship at locus i

$\frac{h_i}{u_i}$: LR of the combination comparing half-sibship to unrelated at locus i

$\frac{f_i}{u_i}$: LR of the combination comparing full-sibship to unrelated at locus i

Obviously, $\frac{f_i}{u_i} = \frac{f_i}{h_i} \cdot \frac{h_i}{u_i}$. Because LR has an approximate logarithmic normal distribution

under the assumption that the loci are independent of each other, the values of $\log_{10}(LR)$ were used for analyses (Nata et al. 1993).

Accumulated $\log_{10}LR$ are computed as follows;

$$\begin{aligned}\frac{F}{H} &= \log_{10} \prod_{i=1}^{10} \frac{f_i}{h_i} = \sum_{i=1}^{10} \log_{10} \frac{f_i}{h_i} \\ \frac{H}{U} &= \log_{10} \prod_{i=1}^{10} \frac{h_i}{u_i} = \sum_{i=1}^{10} \log_{10} \frac{h_i}{u_i} \\ \frac{F}{U} &= \log_{10} \prod_{i=1}^{10} \frac{f_i}{u_i} = \sum_{i=1}^{10} \log_{10} \frac{f_i}{u_i}\end{aligned}$$

Then expected values (E) and variances (Var) are;

$$E\left(\frac{F}{U}\right) = \sum_{i=1}^{10} E\left(\log_{10} \frac{f_i}{u_i}\right)$$

and

$$\begin{aligned}Var\left(\frac{F}{U}\right) &= \sum_{i=1}^{10} E\left(\left[\log_{10} \frac{f_i}{u_i}\right]^2\right) \\ &\quad + 2 \sum_{i=1}^{10} \sum_{j=i+1}^{10} E\left(\log_{10} \frac{f_i}{u_i} \log_{10} \frac{f_j}{u_j}\right) \\ &\quad - \left(\sum_{i=1}^{10} E\left[\log_{10} \frac{f_i}{u_i}\right]\right)^2\end{aligned}$$

The distributions of each $\frac{f_i}{h_i}$, $\frac{h_i}{u_i}$ and $\frac{f_i}{u_i}$ depend on the allele-frequency distribution for the i th marker. To calculate expected values

TABLE 2. *Conditional frequencies of each combination of genotypes*

Genotypes* of 2 individuals	Frequencies**		
	Full sibship (P _f)	Half sibship (P _h)	Unrelated individuals (P _u)
$PP \times PP$	$\frac{1}{4} \sum_m p_m^2 (pm+1)^2$	$\frac{1}{2} \sum_m p_m^3 (p+1)$	$\sum_m p_m^4$
$PP \times QQ$	$\frac{1}{2} \sum_{m < n} p_m^2 p_n^2$	$\sum_{m < n} p_m^2 p_n^2$	$2 \sum_{m < n} p_m^2 p_n^2$
$PP \times PQ$	$\sum_m p_m^2 (p_m+1)(1-p_m)$	$\sum_m p_m^2 (2p_m+1)(1-p_m)$	$4 \sum_m p_m^3 (1-p_m)$
$PP \times QR$	$\frac{1}{2} \sum_m p_m^2 \{2p_m(p_m-1) - \sum_n p_n^2 + 1\}$	$\sum_m p_m^2 \{2p_m(p_m-1) - \sum_n p_n^2 + 1\}$	$2 \sum_m p_m^2 \{2p_m(p_m-1) - \sum_n p_n^2 + 1\}$
$PQ \times PQ$	$\frac{1}{2} \sum_{m < n} p_m p_n (2p_m p_n + p_m + p_n + 1)$	$\frac{1}{2} \sum_{m < n} p_m p_n (4p_m p_n + p_m + p_n)$	$4 \sum_{m < n} p_m^2 p_n^2$
$PQ \times PR$	$\frac{1}{2} \sum_{m \neq n} p_m p_n (1-p_m-p_n)(2p_m+1)$	$\frac{1}{2} \sum_{m \neq n} p_m p_n (1-p_m-p_n)(4p_m+1)$	$4 \sum_{m < n} p_m p_n (p_m+p_n)(1-p_m-p_n)$
$PQ \times RS$	$\frac{1}{2} \sum_{m < n} p_m p_n \{1-2p_m p_n - 2(p_m+p_n) - (1-p_m-p_n) - \sum_i p_i^2\}$	$\sum_{m < n} p_m p_n \{1-2p_m p_n - 2(p_m+p_n) - (1-p_m-p_n) - \sum_i p_i^2\}$	$2 \sum_{m < n} p_m p_n \{1-2p_m p_n - 2(p_m+p_n) - (1-p_m-p_n) - \sum_i p_i^2\}$

* PP and QQ indicate homozygotes, and PQ , PR , QR and RS indicate heterozygotes.

** p represents frequency of each allele.

and variances of accumulated $\log_{10} LR$ of the markers, expected value of $\log_{10} LR$, and $(\log_{10} LR)^2$ of each locus must be computed by adding all possible combination of genotypes (Table 2).

Let C_i is combination of two genotypes.

Then

$$\begin{aligned}
 E_{\text{full-siblings}} \left(\log_{10} \frac{f_i}{u_i} \right) &= \sum_{k_i} E \left(f_i \cdot \log_{10} \frac{f_i}{u_i} \middle| C_i = k_i \right) \text{ etc.} \\
 E_{\text{full-siblings}} \left(\left(\log_{10} \frac{f_i}{u_i} \right)^2 \right) &= \sum_{k_i} E \left(f_i \cdot \left(\log_{10} \frac{f_i}{u_i} \right)^2 \middle| C_i = k_i \right) \text{ etc.}
 \end{aligned}$$

All calculations were performed using Microsoft Excel 97 software.

IBS scoring method

This test statistic is based on the summation of the identity-by-state allele sharing for a pair of individuals (Lange 1986; Bishop and

Williamson 1990; Ehm and Wagner 1998). If the sum is significantly less than the summation of the expected values of allele sharing for full-sibship calculated by use of the population allele frequencies, then the two individuals are presumed not to be full-siblings. Since no loci analysed in our study were considered to be linked to each other, we employed the algorithm proposed by Ehm and Wagner (1998) with minor modification.

Let

$$X_i = \begin{cases} 1 : \text{Two individuals share 2 alleles at locus } i \\ 0.5 : \text{Two individuals share 1 allele at locus } i \\ 0 : \text{Two individuals share no alleles at locus } i \end{cases}$$

Accumulated IBS score were the summation of the score of each locus.

Then

$$Y = \sum_{i=1}^{10} X_i$$

Arithmetic mean ($E[Y]$) and variation of Y were also computed as described by Ehm and

Wagner (1998).

Computer simulation

To evaluate the sibshipwide power of the tests, we generated 10 000 pedigrees using random numbers under two models. Under the full-sib model, each pedigree consisting of two parents and two siblings all typed on the markers using random numbers based on the alleles frequencies. Whereas, under the half-sib model, each pedigree consists of three parents and two children, in which the children share one parent. For the unrelated individual model, 10 000 pair of unrelated persons were also generated randomly. In this simulation, probabilities of the mutations and typing errors were neglected. Accumulated $\log_{10}LR$ and IBS scores were calculated and the mean, variance, and p -value was determined by use of normal distribution for each group. Normality of the data were confirmed by the Kolmogorov-Smirnov two-sample test. To evaluate the

detection power of the tests, upper and lower 5% points ($\alpha=0.05$) of the distribution of each group were designated as the point of discrimination.

RESULTS

LR method

Figs. 1-3 show the distribution of LR in the simulation. Mean and standard deviations of accumulated $\log_{10}LR$ of each group observed in the simulation closely coincided with arithmetical (expected) ones calculated under the assumption that $\log_{10}LR$ have a normal distribution. The normality was confirmed arithmetically ($p>0.9$ each, by the Kolmogorov-Smirnov test) and would also be ascertained with histograms of $\log_{10}LR$ derived from the simulation study (Figs. 1-3). Observed power to detect half-siblings and unrelated individuals as non-full-sib pairs was 0.494 and 0.919, respectively, when nominal (calculated) $\alpha=0.05$ (Table 3). Note that these tests were one sided,

Fig. 1. Distribution of common logarithms of the likelihood ratio ($\log_{10}LR$) of full- to half-sibship (F/H) of each group (white columns: full-siblings, black columns: half-siblings) generated in the simulation. Observed and expected mean $\pm$ s.d. of $\log_{10}LR$ in full-siblings were 0.787 ± 0.929 and 0.799 ± 0.916 , respectively, whereas those of half-siblings were -0.643 ± 0.673 and -0.643 ± 0.661 , respectively.

Fig. 2. Distribution of common logarithms of the likelihood ratio ($\log_{10}LR$) of half-sibship to unrelated individuals (H/U) of each group (white columns: half-siblings, black columns: unrelated individuals) generated in the simulation. Observed and expected mean $\pm$ s.d. of $\log_{10}LR$ in half-siblings were 0.685 ± 0.851 and 0.690 ± 0.838 , respectively, whereas those of unrelated individuals were -0.614 ± 0.758 and -0.612 ± 0.694 , respectively.

Fig. 3. Distribution of common logarithms of the likelihood ratio ($\log_{10}LR$) of full-sibship to unrelated individuals (F/U) of each group (white columns: full-siblings, black columns: unrelated individuals) generated in the simulation. Observed and expected mean $\pm$ s.d. of $\log_{10}LR$ in full-siblings were 2.515 ± 1.684 and 2.545 ± 1.665 , respectively, whereas those of unrelated individuals were -2.022 ± 1.286 and -2.050 ± 1.195 , respectively.

TABLE 3. *Comparison of distribution of each group in LR method*

Nominal*		$\log_{10} LR$	Observed (percentile)		
			Unrelated individuals	Half-siblings	Full-siblings
$\frac{F}{H}$	5 percentile of full-siblings	-0.707	—	49.4	4.7
	95 percentile of half-siblings	0.446	—	93.5	37.1
$\frac{H}{N}$	5 percentile of half-siblings	-0.683	48.1	4.2	—
	95 percentile of unrelated individuals	0.531	93.2	44.5	—
$\frac{F}{N}$	5 percentile of full-siblings	-0.196	91.9	—	4.9
	95 percentile of unrelated individuals	-0.076	93.1	—	5.8

* Based on theoretically derived normal distribution for $\log_{10} LR$.

Fig. 4. Distribution of the sum of Identity-by-State (IBS) scores of each group (white columns: full-siblings, hatched columns: half-siblings, black columns: unrelated individuals) generated in the simulation. Observed and expected mean $\pm$ s.d. of IBS scores of full-siblings were 6.45 ± 1.02 and 6.46 ± 1.00 , those of half-siblings were 4.85 ± 0.96 and 4.85 ± 0.93 , and those of unrelated individuals were 3.55 ± 1.05 and 3.53 ± 0.97 , respectively.

since LR of half-siblings and unrelated individuals must be smaller than that of full-siblings. The power to detect unrelated individuals as non-half-siblings was 0.481 ($\alpha = 0.05$). LR of full-sibship to unrelated (F/U) exceeded 100 in more than 60% of full-sib pairs

generated by simulation, as compared to only 0.2% of unrelated individuals.

IBS scoring method

Each histogram of the simulation data of IBS scores had approximate normality ($\alpha > 0.9$

TABLE 4. *Comparison of distribution of each group in IBS scoring method*

		5 percentile of		95 percentile of	
		Half-siblings	Full-siblings	Unrelated individuals	Half-siblings
Nominal*					
(IBS score)		3.33	4.84	5.15	6.39
	Full-siblings	—	4.8	12.2	41.3
Observed	Half-siblings	4.5	45.6	66.0	93.1
(percentile)	Unrelated	39.7	86.9	94.7	—

* Based on theoretically derived normal distribution for IBS score.

each) with considerable differences between the means (Fig 4). The observed statistical data of IBS scores were also similar to expected values. When a nominal $\alpha = 0.05$ was assumed, the power to detect half-siblings and unrelated individuals as non-full-sib pairs was 0.456 and 0.869, respectively, whereas that to detect unrelated individuals as non-half-siblings was 0.397 (Table 4).

DISCUSSION

Availability of a number of highly polymorphic DNA markers has enabled us to obtain reliable information on probability of sibship. Because sib-pair relationship can not be excluded by the typing of the simple diallelic genetic marker systems, the probability of sibship should be arithmetically evaluated. The test statistics based on summation, over large number of genetic markers, of the number of alleles shared have been proposed and utilized for mapping or linkage analyses, and recently employed to detect typing or pedigree errors in the field of genetics (Lange 1986; Thomson 1986; Bishop and Williamson 1990; Ehm and Wagner 1998). Although the IBS method has not been designed for forensic purpose, this algorithm could also be applicable to the forensic sib-pair tests because of its simplicity comparing to the LR method which currently accepted (Brenner 1997).

The data obtained using simulation indicate that the IBS scoring method, however were

slightly less accurate in detecting the genetic relationship of the affected pair than the LR method. The latter had 91.9% power to detect unrelated individuals and 49.4% power to detect half-siblings as non full-siblings with a nominal 5% false-positive rate (Table 3), whereas the former had 86.9% and 45.6% powers (Table 4), respectively. Similarly, the upper tail of the distribution curve of IBS score of the unrelated individuals would cover a larger area of the curves of full or half-siblings than that of $\log_{10} LR$. As the locus becomes more heterogeneous and polymorphic, the value of LR tends to shift more extremely since gene frequencies are built in the calculation of LR (Table 2). This would be one of the major reasons that the LR method surpassed the IBS method on the sib-pair tests analyzing a relatively small number of polymorphic DNA markers. The power of the IBS method, however, is also greatly influenced by the polymorphism of the markers. If all alleles had the same allele frequencies at each locus, the power of both methods should be essentially identical. Furthermore, Ehm and Wagner (1998) have stated that the IBS method using 50 unlinked markers has 100% power to detect unrelated individuals as not full-siblings, with a 5% false-positive rate.

In this study, we have ignored the possibility of mutation. Several studies pointed out that mutation at STR loci were considered to be rare but not negligible for paternity testing (Weber and Wong 1993; Brinkmann et al. 1998). When

LR for paternity is calculated taking into account the possibility of mutation, inconsistent locus deserves a very small LR in paternity testing. Therefore, a mutation event produces a great effect on the values of accumulate LR for paternity. On the other hand, no inconsistency exists on allele sharing patterns between siblings, and LR for full-siblings to unrelated (F/U) were no less than 0.25 even if the two individuals share no allele (Table 2). Thus, it should not be so convincing that IBS scoring method would be more robust against mutation than LR method with regard to the sib-pair tests.

A significant advantage of the LR method over IBS method was observed on the detection rate of unrelated individuals as not half-siblings; i.e., 0.481 vs. 0.397 when nominal $\alpha = 0.05$ (Tables 3 and 4). This is partly due to the particular marker system employed in this study. Observed mean of IBS score of the half-siblings was 4.85 sharing an average of 0.99 allele per locus and 81% of them had IBS score between 4 and 6. If a pair shares 1 allele, the likelihood of half-sibship becomes even grater than that of full-sibship, resulting increase of LR comparing half-sibship to unrelated (Table 1).

The results of this study suggested the validity of the LR method. On the other hand, if a sufficient number of highly polymorphic markers are available, the IBS scoring method would be also an informative tool, but still an inferior tool, for the sib-pair tests.

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