Letters to the Editor

Am. J. Hum. Genet. 67:527, 2000

Another Look Back

To the Editor:

The most interesting and informative "A Look Back" by your predecessor, Peter H. Byers, which appeared in the December 1999 issue of the Journal (pp. 1487–1488), contained an error that needs correction. You were introduced as "the first nonclinician to edit the *Journal,*" and this was considered by Dr. Byers to be one of the factors boding well for the journal.

One of the most distinguished previous editors, Arthur G. Steinberg (A.G.S.), was also a nonclinician, with a Ph.D. in *Drosophila* genetics from Columbia University. During his term as Editor, beginning with Volume 8 (1956) and ending with Volume 13 (1961), the discipline of human genetics underwent dramatic changes as it grew enormously. In looking back on his period as Editor, Steinberg (1995) analyzed the topics most often reported on and found that they were "blood groups, various diseases, population genetics, statistical methods in human genetics, mutations and linkage." He also relates how he became disturbed by some of the reviews submitted by referees and therefore ruled that referees would no longer be anonymous. Although "the reviews were greatly improved the referees were not happy with my objection to anonymity" and "the policy was abandoned by my successor and has remained so."

In an "Appreciation" of A.G.S. (Fraser et al. 1995), we learn from Alexander G. Bearn that A.G.S. served on the Board of Directors of the American Society of Human Genetics for 10 years and became its president in 1964. A.G.S. was also the founding editor of *Progress in Medical Genetics* (the first volume appeared in 1961), and, in the following year, Alexander Bearn joined him as coeditor of the publication, which continued through 16 volumes (a span of 22 years) before the editorship passed into the hands of Barton Childs, Neil A. Holtzman, Haig H. Kazazian, Jr., and David L. Valle. John M. Opitz, in the same Appreciation, ranks A.G.S. as one of the greatest editors in the field of human genetics, with Penrose and Cotterman.

Arthur Steinberg is alive and well and living in Cleveland, having retired in 1982 from the Department of Biology at Case Western Reserve University (CWRU). He has recently been honored by CWRU, from which he received the 1999 Frank and Dorothy Hovorka Prize, recognizing "outstanding achievements in teaching, research, and scholarly service which have benefited the community, nation, and world."

Arthur told me some years ago that he stopped attending congresses when the mention of his name occasioned one of two responses, "Steinberg, Steinberg. Never heard of him!" or "Steinberg. Is he still alive?"

I should like to take this opportunity of wishing you, the new Editor of the *Journal,* a happy and fulfilling term of office. The fact that you are not the **first** nonclinician to be appointed Editor can in no way detract from your qualifications to fill the role with distinction!

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0002-9297/2000/6702-0033$02.00

Am. J. Hum. Genet. 67:527–528, 2000

Reply to Jenkins

To the Editor:

Dr. Jenkins is not the only person to have recognized my mistakes concerning the publisher and the doctoral degrees of the previous Editors of the *Journal.* Several

previous Editors had Ph.D. degrees, including the founding Editor, C. W. Cotterman (University of California, 1949–51) and several successors: Herluf Strandskov (University of Chicago, 1952–54), Lawrence H. Snyder (University of Oklahoma, 1955), and Arthur G. Steinberg (Children's Cancer Research Fund, Boston and Western Reserve University, 1956–61). C. Nash Herndon (Bowman Gray School of Medicine, 1962–64) appears to have been the first editor who was a physician, followed by H. Eldon Sutton, Ph.D. (University of Texas, 1965–69), and then by several people with medical degrees—Arno G. Motulsky (University of Washington, 1970–75), William J. Mellman (University of Pennsylvania, 1976–78), David Comings (City of Hope, Duarte, 1979–86), Charles J. Epstein (University of California at San Francisco, 1987–93), and Peter H. Byers (University of Washington, 1994–2000). Steve Warren is the first Editor, *in a while,* with a Ph.D.

The *Journal* was published by Waverly Press, Baltimore, during 1949–62 and by Grune and Stratton from several locations from 1963–67. The University of Chicago Press began publishing the *Journal* in 1968.

I appreciate the enthusiasm with which many people remember the early days of the *Journal* and their vigor in protecting its integrity. Even Editors need fact checkers from time to time. My thanks go to all those who served the role in this instance and in others.

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0002-9297/2000/6702-0034$02.00

Am. J. Hum. Genet. 67:528–531, 2000

Age and Origin of the *PRNP* E200K Mutation Causing Familial Creutzfeldt-Jacob Disease in Libyan Jews

To the Editor:

Creutzfeldt-Jacob disease (CJD [MIM 123400]), the most prevalent of the human spongiform encephalopathies (HSEs), is a rapidly progressive neurodegenerative disease that manifests itself as a sporadic, transmissible, or familial disorder (Johnson and Gibbs 1998). Patients with CJD generally develop neurological dysfunction in midlife and die within 6–24 mo of onset. The largest cluster of CJD occurs among Libyan Jews, where the incidence (1/10,000) is ~100 times higher than incidence worldwide. The origin of the higher incidence of CJD in this population is an intriguing problem that has not yet been resolved.

Although a few studies (reviewed in Meiner et al. 1997) had pointed out the familial predisposition to CJD, it was first speculated that its frequency in Libyan Jews could be explained by their habit of consuming lightly grilled sheep's brains or eyeballs (Herzberg et al. 1974; Alter and Kahana 1976), reflecting a shared en-

Table 1

Estimation of the Age of the E200K Mutation in the *PRNP* Gene, Causing CJD in Libyan Jews (Risch et al.'s [1995] Method, without and with the Luria-Delbrück Correction for Population Growth Rate [Labuda et al. 1996])

	Distance from *PRNP* locus[a]				Haplotype data[b]		LD[c]	Estimated age[d]		
Marker	Mb	cM	θ	Allele	p_d	p_n	(δ)	g	g_0	g_c
D20S116	.57	2.11	.0211	20	.81	.29	.73	14.6	6.3	20.9
D20S482	.27	1	.001	14	.93	.59	.83	18.6	12.4	31
D20S895	.35	1.3	.013	18+19	.87	.35	.8	17.1	7.3	24.4

[a] Genetic distances (in centimorgans) were calculated using a conversion factor of 3.7 cM/Mb obtained from regression of centimorgan vs. megabyte values for 20p12-pter loci (mapping data are from LDB).

[b] p_d and p_n are the frequencies for the marker allele on disease-mutation–bearing and normal chromosomes, respectively. Source of data: table 2 of Lee et al. (1999).

[c] Linkage disequilibrium index, calculated according to Bengtsson and Thompson (1981): $\delta = (p_d - p_n)/(1 - p_n)$.

[d] g and g_c are the estimated number of generations obtained by use of Risch et al.'s (1995) algorithm, without and with the Luria-Delbrück correction of the genetic clock (Labuda et al. 1996), respectively: $g = \log\delta/\log(-\theta)$ and $g_c = g + g_0$, where $g_0 = -(1/d)\ln(\theta \times f_d)$, assuming $d = 0.5$ and $f_d = 1/d$.

vironmental risk (exposure to scrapie-infected meat) rather than any genetic factor. This hypothesis, based on the unrealistic assumption that scrapie was widespread in Libya and that a marked culinary difference between Jews of Libyan and other North African origins existed, suffered a strong blow when two cases of CJD among young Jews born in Israel to immigrants from Libya were discovered (Nisipeanu et al. 1990; Hsiao et al. 1991). They could not have been exposed to scrapie, since it does not exist in Israel. The most likely explanation soon became that CJD could be inherited genetically in a pattern similar to that of another HSE, Gerstmann-Sträussler-Scheinker disease (MIM 137440). Genetic linkage between a missense mutation (E200K: 598A→G; 200Glu→Lys) in the prion protein (*PRNP*) gene and CJD was established in Libyan Jews (LOD score >4.85 [Gabizon et al. 1993]). The E200K mutation, which accounts for >70% of cases of familial CJD, was first identified in a Polish family and subsequently in patients living in England, France, Austria, Slovakia, Chile, the United States, and Japan. The analysis of its geographic distribution (Goldfarb et al. 1991) suggested that the E200K mutation originated in Spain >5 centuries ago, possibly in a Jewish person, and spread to Mediterranean and continental countries after the expulsion of Sephardic Jews from Spain. The hypothesis of propagation through a limited number of successful migrants was supported by the discovery of a higher frequency, in patients with CJD and their unaffected relatives, compared with the general Libyan Jewish population, of *PRNP*'s 129M polymorphism in the normal allele. However, the same hypothesis was disputed (Gabizon et al. 1993; Korczyn 1994) on the basis of lack of evidence for the presence of the E200K mutation in Spain and among Jews living in other countries to which Sephardim have emigrated and because it seems to disregard the intermarriage rules followed by the local Jewish communities.

Recently, the E200K mutation has been discovered in other European countries—that is, in Italy, as well as in Spain itself. More decisively, Lee et al. (1999) reported in the *Journal* that Libyan, Tunisian, Italian (continen-

Table 2

Estimation of the Age of the E200K Mutation in the *PRNP* Gene, Causing CJD in Libyan Jews (Reich and Goldstein's [1999] Iterative Method, without and with the Luria-Delbrück Correction for Population Growth Rate [Labuda et al. 1996])

	Distance from *PRNP* locus[a]				Mutation data[b]		Haplotype data[c]		Estimated age[d]		
Marker	Mb	cM	θ	Allele	μ	f	p_d	p_n	g	g_0	g_c
D20S116	.57	2.11	.0211	20	.00056	.32	.81	.29	14	6.3	20.3
D20S482	.27	1	.001	14	.0021	.29	.93	.59	12	12.4	24.4
D20S895	.35	1.3	.013	18+19	.00056	.09	.87	.35	16	7.3	23.3

[a] See footnote a to table 1.

[b] μ is the assumed frequency of mutation at the marker locus (dinucleotide repeats [D20S116 and D20S482], $\mu \approx .00056$; tetranucleotide repeat [D20S482], $\mu \approx .0021$; Weber and Wong 1993) and f is the observed frequency of all one-mutant neighbors of the ancestral allele in the control population (source of data, table 1 of Lee et al. 1999).

[c] See footnote b to table 1.

[d] g and g_c are the estimated number of generations obtained by use of Reich and Goldstein's (1999) algorithm, without and with the Luria-Delbrück correction of the genetic clock (Labuda et al. 1996), respectively. To provide a complete model for the haplotype's evolutionary process, according to the method of Reich and Goldstein (1999), a Markov transition matrix (**K**) for each marker was generated, which gives the probabilities that any one haplotype will be transformed into any other one in a single generation. **K** was calculated as the weighted sum of matrices corresponding to recombination (**R**), mutation (**M**), and no event occurring (**I**): $\mathbf{K} = \theta\mathbf{R} + \mu\mathbf{M} + (1 - \theta - \mu)\mathbf{I}$, where μ is the frequency of mutation at the marker locus. The matrix **R** has the elements $R_{11} = p_n$, $R_{12} = p_n$, $R_{21} = 1 - p_n$, and $R_{22} = 1 - p_n$. Under the assumption of a stepwise mutation model for microsatellites (Goldstein and Pollock 1997) and a distribution of marker allele sizes on disease chromosomes that matches that seen in the control population, **M** has the elements $M_{11} = 0$, $M_{12} = f/2$, $M_{21} = 1$, and $M_{22} = 1 - f/2$, where f is the frequency of all one-mutant neighbors of the ancestral allele in the control population. With the parameters of **K** specified, the number of generations that have passed since the foundation event was estimated by multiplying the state vector $(q, 1 - q)$ by **K** iteratively, until the observed proportion of ancestral haplotypes was reached ($q \approx p_d$). Iteration began at a frequency vector of (1,0), corresponding to the archetypal condition of only ancestral haplotypes. The number of times that **K** had been multiplied yielded an estimate of g (Reich and Goldstein 1999). The iterative procedure was implemented through the facilities of the SPSSv.9 matrix language. Iterations stopped at an average distance of $\pm 5 \times 10^{-3}$ from the corresponding p_d value, which is the maximum attainable accuracy, being p_d values accurate to $\pm 1 \times 10^{-2}$. The Luria-Delbrück-corrected age (Labuda et al. 1996) is given as $g_c = g + g_0$, where $g_0 = -(1/d)\ln(\theta \times f_d)$, assuming $d = 0.5$ and $f_d = 1/d$.

tal), Chilean, and Spanish families with CJD share a major haplotype on chromosome 20p12-pter, to which the *PRNP* gene has been mapped, whereas families with CJD from Germany, Sicily, Austria, and Japan bear different corresponding haplotypes, suggesting independent mutational events. The prominence of this study for the reinstatement of the "founder effect" hypothesis to explain the Libyan focus of familial CJD cannot be dismissed. However, the probational strength of haplotype data presented by Lee et al. (1999) can be even more convincing if they are quantitatively analyzed for linkage disequilibrium (LD) decay over time and the results compared with the Libyan Jewish population's history. To perform this, two different methods were used, both of which are based on the genetic clock equation $\ln P = -\theta g$, relating the time (in generations, g) tracing back to the most recent common ancestor of mutant chromosomes, the frequency of recombination between the disease locus and the marker (θ), and the probability that a marker's allele on a disease chromosome is the ancestral one (P). Taking the frequencies on E200K-bearing (p_d) and normal (p_n) Libyan Jewish chromosomes for the alleles of three microsatellite markers flanking the *PRNP* locus and defining the putative common ancestral haplotype (D20S116–20, D20S482–14, and D20S895–18/19; table 2 of Lee et al. 1999), the LD measure, $\delta = (p_d - p_n)/(1 - p_n)$, was calculated according to Bengtsson and Thomson (1981). Recombination fraction values (θ) were conveniently estimated from chromosome-20 physical mapping (LDB and The Sanger Centre) under the assumption of a genetic to physical distance ratio of 3.7 obtained from regression of centimorgan versus megabyte values for 20p12-pter loci. Applying the algorithm of Risch et al. (1995), $g = \log \delta / \log (1 - \theta)$, the estimated age (in generations, g) of the E200K mutation is 16.8 ± 2.0 SD (95% confidence interval [CI] 11.7–21.8 g) (table 1). Using the iterative method of Reich and Goldstein (1999), which models the regeneration of the ancestral haplotype by the recombination and mutation process through a Markov transition matrix that gives the probabilities that any one haplotype will be transformed into any other one in a single generation, a somewhat lower age was obtained (14 ± 2 SD; 95% CI 9–19 g; table 2). When supplemented by setting the genetic clock according to the Luria-Delbrück approach (Labuda et al. 1996), under the assumption of a mean population growth rate of .5, the estimate rises to 22.7 ± 2.1 SD (95% CI 17.4–27.9 g). Given an intergenerational interval of 30 years (Tremblay and Vézina 2000) and an average year of birth of 1950 for all affected and carrier subjects, the present results would date the most recent common ancestor bearing the E200K mutation back to 1450–1530 or to the second half of the 13th century. This dating points to the origin of CJD in Libyan Jews at the time, or before, that Jewish families of Iberian origin settled in Libya after their expulsion from Spain in 1492 and from Portugal in 1497 (Barnavi 1992). Intrafamily marriages were a common practice among them (Gabizon et al. 1993), and a constant growth of this isolated population in the centuries after immigration has been documented (see, e.g., Goldberg 1971). However, other events, such as immigration of Jews from the neighboring island of Jerba at approximately the same time (Udovitch and Valensi 1984) or bottleneck effects, should be taken into consideration. Despite the methodological limits associated with LD-based allele age estimation, persuasive further evidence for the hypothesis of a "Spanish founder effect" in Libyan Jewish CJD genetic epidemiology can be drawn from the analysis of the haplotype data reported by Lee et al. (1999).

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

LDB, the Genetic Location Database, Department of Human Genetics, University of Southampton, UK, http://cedar.genetics.soton.ac.uk/public_html/ldb.html

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for CJD [MIM 123400] and Gerstmann-Sträussler-Scheinker disease [MIM 137440])

Sanger Centre, The, http://webace.sanger.ac.uk/cgi-bin/ace/simple/

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0002-9297/2000/6702-0035$02.00

Am. J. Hum. Genet. 67:531–534, 2000

The Disequilibrium Maximum-Likelihood–Binomial Test Does Not Replace the Transmission/ Disequilibrium Test

To the Editor:

In a previous issue of the *Journal,* Huang and Jiang (1999) introduced the disequilibrium maximum-likelihood–binomial test (DMLB) for affected-sibship data. The DMLB is supposed to combine the advantages of the mean test (Blackwelder and Elston 1985) and the transmission/disequilibrium test (TDT) (Terwilliger and Ott 1992; Spielman et al. 1993), in that the DMLB performs well when linkage disequilibrium (LD) is low and has power higher than or equal to that of the TDT when the LD ranges from moderate to strong. If this claim was correct, the TDT would be obsolete. In this letter, we show how to compute exact *P* values and exact critical values for the DMLB (and for the TDT), and we show that, when these exact critical values are used, the DMLB is never significantly more powerful than the TDT when there is complete LD. The opposite is true: the TDT is often significantly more powerful than the DMLB. Even when LD is at 80% of its maximum, the TDT still outperforms the DMLB when the marker- and disease-allele frequencies are identical. The asymptotic approximation used by Huang and Jiang (1999) can be inaccurate. We show that their choice of the critical value for the DMLB (c_{DMLB}) is often anticonservative—that is, it violates the false-positive rate—whereas their choice of the critical value for the TDT (c_{TDT}) tends to be overly conservative. The exact critical values depend on the number of heterozygous parents in the sample, and we are making available (contact the corresponding author) an SAS Institute (1990) program that computes exact critical values. Huang and Jiang (1999) introduce DMLB tests for two different cases of hypotheses. For the sake

Table 1

Exact Error Rates of the DMLB and the TDT Test Statistics When the Critical Values (Corresponding to $\alpha = .0001$) Proposed by Huang and Jiang (1999) Are Used

n_2	P(DMLB > 17.38)	P(TDT > 15.14)
30	.0001544	.0000422
50	.0001585	.0000785
100	.0001475	.0000913
300	.0001269	.0001019
500	.0001237	.0000985
700	.0001220	.0001051
1,000	.0001158	.0000902

NOTE.—The DMLB critical value obviously is anticonservative.

Table 2

Exact Critical Values for the TDT and the DMLB Corresponding to α, as a Function of n_2

	Exact Values at α =							
	.0001		.001		.01		.05	
n_2	c_{DMLB}	c_{TDT}	c_{DMLB}	c_{TDT}	c_{DMLB}	c_{TDT}	c_{DMLB}	c_{TDT}
30	19.63	15.03	13.43	11.30	8.63	6.70	5.43	4.30
50	18.94	14.46	13.70	10.26	8.38	6.78	5.18	4.02
100	18.17	14.59	13.51	10.59	8.57	6.49	5.29	3.93
300	18.00	15.36	13.12	10.67	8.40	6.83	5.23	3.84

of brevity, we will focus only on the more important two-sided hypothesis, which is relevant when there is no prior knowledge about which marker allele is in LD with the disease. Let us give a brief description of the TDT and the DMLB for families with two affected children. Suppose that there are n_2 heterozygous B_1B_2 parents in the data set. Let n_{22} denote the number of heterozygous parents who transmitted allele B_1 to both children, let n_{21} denote the number of heterozygous parents who transmitted B_1 to one child and B_2 to the other child, and let n_{20} denote the number of heterozygous parents who transmitted B_2 to both children. Then the TDT statistic is given by $\text{TDT} = [2\,(n_{22} - n_{20})^2]/n_2$ with an asymptotic χ_1^2 distribution under the null hypothesis of no linkage. The score-statistic version of the DMLB is given by

$$\text{DMLB} = \begin{cases} \dfrac{2(n_{22} - n_{20})^2}{n_2} & \text{if } n_{20} + n_{22} \leqslant n_{21} \\ \dfrac{(n_{20} + n_{22} - n_{21})^2 + 2(n_{22} - n_{20})^2}{n_2} & \text{if } n_{20} + n_{22} > n_{21} \end{cases}.$$

Incidentally, we note that $[(n_{20} + n_{22} - n_{21})^2]/n_2$ equals the mean test for these data. Huang and Jiang (1999) show that, under the null hypothesis of no linkage, the DMLB has the asymptotic distribution $.5\chi_1^2 + .5\chi_2^2$. They use this asymptotic distribution to compute the critical value $c_{\text{DMLB}} = 17.38$, corresponding to a false-positive rate of $\alpha = .0001$. Similarly, under the null hypothesis of no linkage, the TDT has an asymptotic χ_1^2 distribution, which can be used to show that, for the same false-positive rate, the critical value of the TDT is given by

Table 3

Comparison of the Power of the DMLB with That of the TDT, When $\alpha = .0001$

	Power for δ_p =											
	1			.8			.5			.3		
Model and p (m)	N	TDT	DMLB	N	TDT	DMLB	N	TDT	DMLB	N	TDT	DMLB
Additive:												
.2 (.2)	51	.82	.75	75	.81	.76	173	.80	.80	437	.80	.87
.5 (.5)	95	.81	.73	154	.81	.75	410	.80	.79	1,000	.70	.77
.1 (.2)	68	.82	.78	100	.81	.79	233	.80	.84	596	.80	.92
.5 (.2)	511	.80	.77	772	.80	.79	1,000	.34	.39	1,000	.04	.08
.2 (.5)	123	.81	.77	196	.80	.80	514	.80	.90	1,000	.54	.89
.1 (.5)	177	.80	.80	281	.80	.83	730	.80	.94	1,000	.30	.83
Dominant:												
.2 (.2)	71	.81	.76	106	.81	.77	250	.80	.81	642	.80	.88
.5 (.5)	288	.80	.76	461	.80	.77	1,000	.66	.67	1,000	.09	.12
.1 (.2)	82	.81	.78	122	.81	.80	287	.80	.85	741	.80	.93
.5 (.2)	1,000	.55	.52	1,000	.26	.26	1,000	.04	.04	1,000	.00	.01
.2 (.5)	188	.81	.79	300	.80	.82	783	.80	.91	1,000	.26	.66
.1 (.5)	225	.80	.80	356	.80	.85	923	.80	.95	1,000	.19	.69
Multiplicative:												
.2 (.2)	25	.84	.78	36	.82	.77	81	.80	.82	201	.80	.91
.5 (.5)	35	.82	.75	61	.82	.79	169	.80	.86	486	.80	.96
.1 (.2)	37	.82	.77	54	.81	.79	123	.81	.86	308	.80	.94
.5 (.2)	235	.80	.82	351	.80	.85	834	.80	.94	1,000	.27	.78
.2 (.5)	50	.82	.78	81	.80	.82	217	.80	.94	612	.80	1.00
.1 (.5)	86	.81	.80	137	.81	.85	357	.80	.96	999	.80	1.00
Recessive:												
.2 (.2)	143	.81	.77	211	.80	.78	493	.80	.81	1,000	.62	.72
.5 (.5)	56	.82	.77	92	.81	.79	247	.80	.84	700	.80	.93
.1 (.2)	1,000	.64	.63	1,000	.33	.33	1,000	.05	.05	1,000	.01	.01
.5 (.2)	326	.81	.80	489	.80	.83	1,000	.69	.85	1,000	.13	.42
.2 (.5)	406	.80	.79	636	.80	.82	1,000	.44	.57	1,000	.06	.16
.1 (.5)	1,000	.06	.05	1,000	.02	.02	1,000	.00	.00	1,000	.00	.00

c_{TDT} = 15.14. These critical values are not ideal, as can be seen from table 1, which lists the exact error rates as a function of the number of heterozygous parents n_2. Fortunately, one does not need to rely on asymptotic approximations, since, under the null hypothesis, one can easily compute exact *P* values for both tests. However, even if one is not interested in exact *P* values, one can easily compute the exact critical values that should be used, for families with two affected offspring, to maintain the correct type I error rate. The key observation for these calculations is that, under the null hypothesis, (n_{22},n_{21},n_{20}) has a multinomial distribution with parameters n_2 and (p_2,p_1,p_0) = (.25,.5,.25), and the DMLB is a simple function of this low-dimensional distribution. These null distributions can be used to compute the exact critical values for both tests, some of which are listed in table 2. The critical values depend on the sample sizes, but there is no monotonous relationship between the number of heterozygous parents n_2 and the critical values. Since interpolation between the different values of n_2 is difficult, we are making available (contact the corresponding author) an SAS Institute (1990) program that calculates the critical values for both tests.

To compare the power of the two tests, we conducted simulation studies for the genetic models studied by Huang and Jiang (1999). We considered four genetic models: additive, dominant, multiplicative, and recessive. Let f_0, f_1, and f_2 be the penetrances of disease genotypes *dd, Dd,* and *DD,* respectively, where *D* is the disease-causing allele. The relative genotypic risks (GRRs) are defined as $r_1 = f_1/f_0$ and $r_2 = f_2/f_0$. Like Huang and Jiang, we considered the following GRR values in the power calculation: (1) for the additive model, r_1 = 4, r_2 = 7; (2) for the dominant model, r_1 = 4, r_2 = 4; (3) for the multiplicative model, r_1 = 4, r_2 = 16; and (4) for the recessive model, r_1 = 1, r_2 = 4. We assumed that the biallelic marker and the disease loci are tightly linked (θ = 0), and we studied two marker-allele frequencies *m* (.2 and .5) and three disease-allele frequencies *p* (.1, .2, and .5). We looked at four different values (1, .80, .50, and .30) of the normalized LD $\delta_p = \Delta/\Delta_{max}$, where $\Delta = P(B_1D) - mp$ and $\Delta_{max} = \min[(1-m)p, m(1-p)]$. For each genetic model, we determined the approximate number of families *N* required to yield 80% power for the TDT (Knapp 1999). If $N < 1{,}000$, then we simulated 100,000 replicates of *N* families; however, if $N > 1{,}000$, then each sample was limited to 1,000 families. Both tests were evaluated for the same replicates. For each replicate, we determined the number n_2 of heterozygous parents in the sample and then used it to compute exact critical values for both tests. Since both tests have a discrete distribution, we used a randomized test to reject at an exact false-positive rate of α = .0001.

Table 3 lists the results of our simulation studies. When the marker-allele frequency equals the disease-allele frequency ($m = p$), the TDT has more power than the DMLB when $\delta_p \geq .8$. Even when $\delta_p = .5$, the DMLB is not consistently more powerful than the TDT.

When $m \neq p$ and $\delta_p = 1$, the TDT is more powerful than the DMLB in all but one case (multiplicative, p = .5, m = .2). However, when $\delta_p = .8$, the DMLB is, "on average," more powerful than the TDT. When $\delta_p \leq .5$, the DMLB is usually more powerful than the TDT. However, in many cases in which the DMLB is significantly more powerful than the TDT, the required sample sizes are unrealistic (>1,000 families) anyway. Therefore, neither test would be useful in such a setting.

We conclude that, even though tests that can adapt to the degree of LD are a good idea, our simulations have shown that, if the degree of LD is strong ($\delta_p \geq$ .80), the DMLB usually is not more powerful than the TDT. For a candidate-gene study in which the typed marker affects the disease risk (i.e., $m = p$ and $\delta_p = 1$), the TDT is preferable to the DMLB. In their study, Huang and Jiang (1999) showed that, when the LD is very weak, the mean test has more power than the DMLB. Therefore, the DMLB is most useful when there is moderate LD between marker and disease locus. Unfortunately, in practice, the amount of LD is usually unknown.

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0002-9297/2000/6702-0036$02.00

Am. J. Hum. Genet. 67:534, 2000

Reply to Horvath et al.

To the Editor:

The letter by Horvath et al. points out that the critical value based on the asymptotic distribution of the disequilibrium maximum-binomial likelihood (DMLB) test (Huang and Jiang 1999) is anticonservative. They show, on the basis of the exact critical values that they obtained, for affected-sib-pair data and the models considered in the study by Huang and Jiang (1999), that (1) when $\delta_p = 1$, the transmission/disequilibrium test (TDT [Falk and Rubinstein 1987; Terwilliger and Ott 1992; Spielman and Ewens 1993]) is more powerful than the DMLB, except in one case; (2) when $\delta_p = .8$ and $p = m$, the TDT is more powerful than the DMLB; (3) when $\delta_p = .8$, the DMLB is, "on average," more powerful than the TDT; and (4) when $\delta_p = .5$ or .3, the DMLB is more powerful than the TDT, except in one case.

We thank Horvath et al. for carrying out the exact calculation of the critical values of the DMLB and for pointing out the anticonservativeness of the asymptotic approximation used in our report. We agree that exact calculation should be used whenever possible. There are several points on which we would like to comment in this reply. First, in our report, we did not suggest that the DMLB should replace the TDT or any other linkage test. However, we believe that, in addition to the existing methods, the DMLB is an interesting approach when the extent of linkage disequilibrium (LD) is unknown. Second, we stated in our report that, when LD is maximum or nearly so, the power of the DMLB and that of the TDT are similar. The results by Horvath et al. show that, when $\delta_p = 1$, although the TDT tends to be more powerful than the DMLB, the difference in power is often not large. The median of the differences is .035; ~75% of the differences are <.05. The largest difference is .08, which occurs in one case. Third, the letter by Horvath et al. does not give a complete picture of the comparison. They did not compare the power of the TDT versus that of the DMLB, for any values of δ_p in the range $0 \leqslant \delta_p < .3$. In this range, the DMLB is more powerful than the TDT. When the extent of LD is unknown, meaningful conclusions regarding the comparison of any two linkage tests should be drawn on the basis of the consideration of the full range of LD, not just part of the range. Fourth, both our calculation and that by Horvath et al. are approximate with respect to the original likelihood-ratio form of the DMLB (eq. [7]) in Huang and Jiang 1999), because they are based on its score test statistic.

Horvath et al. also mentioned the case of candidate-gene study and the situation when LD is very weak. If we know the amount of LD, we should build this information into the analysis. For instance, in a candidate-gene study, we can fix the mixture parameter λ at 1 and 0 for a two-sided test in the DMLB likelihood (λ is defined in Huang and Jiang 1999). If we know that LD is very weak, we can let $\lambda = .5$ in the DMLB likelihood. In either case, it results in reduced degrees of freedom and increased power. However, the point of our report is to adaptively detect linkage when the amount of LD is unknown, such as when one is conducting a genomewide screen. The extent of LD may vary across different chromosome regions. Because the DMLB tends to be more powerful than the TDT when $0 \leqslant \delta_p \lesssim .8$ and only slightly less powerful than the TDT when $\sim .8 < \delta_p \leqslant 1$, we believe that the overall conclusion of our report remains valid—that is, the DMLB has relatively robust and good power behavior in comparison with the TDT, when the whole range of LD is considered.

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0002-9297/2000/6702-0037$02.00

Am. J. Hum. Genet. 67:535–537, 2000

Pseudoautosomal Linkage of Hodgkin Disease

To the Editor:

We wish to thank Horwitz and Wiernik for their interesting paper "Pseudoautosomal Linkage of Hodgkin Disease" (Horwitz and Wiernik 1999), even though we disagree with some of their conclusions. The authors combined two findings from the literature to propose a new direction in the genetic epidemiology of Hodgkin disease. The first finding is that of a pair of sisters concordant for both Hodgkin disease (MIM 236000) and the rare disorder Leri-Weill dyschondrosteosis (LWD) (MIM 127300) (Gokhale et al. 1995). The second finding is that LWD results from mutations and large deletions of the SHOX homeobox gene on the pseudoautosomal region of the short arms of the X and Y chromosomes (Belin et al. 1998; Shears et al. 1998). Horwitz and Wiernik conjecture that a gene for Hodgkin disease may also lie in this region.

This conjecture predicts an excess of sex concordance among pairs of relatives with Hodgkin disease, an excess that, in fact, has been reported for sibs (Grufferman et al. 1977). To investigate this prediction in a larger data set, Horwitz and Wiernik evaluated sex concordance in 102 affected sib pairs (ASPs) gathered from the world's literature. They found that 63 (62%) of the pairs were concordant (41 male-male and 22 female-female). Part of this excess concordance is likely explained by the higher incidence of Hodgkin disease among males than among females. After allowing for this fact, the authors conclude that the excess concordance is not statistically significant. They base their conclusion on the value 4.40 of a χ^2 test on 2 df ($P > .2$). In fact, the excess is statistically significant, because the value 4.40 of the likelihood ratio statistic of the null hypothesis of no concordance, allowing for a male excess risk, should be referred to a χ^2 distribution on 1 df ($P < .05$).

To further investigate their conjecture, Horwitz and Wiernik conducted a linkage analysis of the pseudoautosomal region, using sexual phenotype as the marker and based on the sex distribution within a sample of multiple-case families obtained from the literature and from Montefiore Medical Center. On the basis of a parametric analysis, the authors report a male recombination fraction (θ) of .254, which they interpret as evidence that the putative Hodgkin disease gene is in close proximity to the SHOX locus. Using an analysis based on the beta model proposed by Morton and colleagues (Morton 1996; Collins and Morton 1996), they conclude that a putative pseudoautosomal region (PAR) gene accounts for 29% of Hodgkin disease heritability in the United States. We believe that the authors have overinterpreted the results of both these analyses.

They have overinterpreted the results of the parametric analysis, because the models they fit to the data fail to account for the probable genetic heterogeneity of the disease. Instead, the models assume that a PAR gene is solely responsible for hereditary Hodgkin disease. It is well known that failure to account for such heterogeneity leads to overestimates of θ. Evidence that more than one gene is responsible for hereditary Hodgkin disease arises not only from data implicating the HLA region (Berberich et al. 1983; Chakravarti et al. 1986), but also from the high recurrence risk in MZ twins compared with DZ twins (Mack et al. 1995). Thus the authors are attributing greater precision to the estimate $\theta_{\text{male}} = .254$ than is warranted by the data.

In an attempt to estimate the fraction of hereditary Hodgkin disease due to a putative PAR gene, Horwitz and Wiernik fit Morton's beta model (Morton 1995; Collins and Morton 1996) to the sexual phenotypes of the 102 ASPs. They combined the estimate for beta obtained in this way with sibling recurrence risks from the literature to produce their 29% estimate. To clarify why this estimate is inappropriate, it is helpful to review the beta model. Suppose that there are m unlinked genes responsible for hereditary Hodgkin disease. The model assumes that the joint probability that two relatives are both affected, given their identical-by-descent (IBD) status for each of the m genes, is

$$P(D_1 = D_2 = 1 \,|\, \text{IBD}_1 = j_1,\ldots,\text{IBD}_m = j_m) = K^2 \exp\left[\sum_{\ell=1}^{m} j_\ell \beta_\ell\right] . \tag{1}$$

In this equation, D_1 and D_2 are indicators for Hodgkin disease status, K is the prevalence of disease in the general population, IBD_ℓ denotes IBD status for gene ℓ, $\ell = 1,\ldots,m$, and $\beta_\ell \geq 0$ measures the log contribution of gene ℓ to the sibs' phenotype correlation, $\ell = 1,\ldots,m$. Equation (1) implies that two sibs are both affected with probability

$$P(D_1 = D_2 = 1 \,|\, \text{sibs}) = K^2 \left[\sum_{j_1=0}^{2} \cdots \sum_{j_m=0}^{2} \pi(j_1,\ldots,j_m) \exp\left(\sum_{\ell=1}^{m} j_\ell \beta_\ell\right)\right] , \tag{2}$$

where

$$\pi(j_1,\ldots,j_m) = \left(\frac{1}{4}\right)^m \prod_{\ell=1}^{m} \binom{2}{j_\ell} \tag{3}$$

is the joint probability that two sibs share j_ℓ alleles IBD at locus ℓ, $\ell = 1,\ldots,m$. Substituting equation (3) into equation (2) gives

$$P(D_1 = D_2 = 1 \mid \text{sibs}) = K^2 \prod_{\ell=1}^{m} \left(\frac{1 + e^{\beta_\ell}}{2}\right)^2 . \qquad (4)$$

Equation (4) determines the sibling recurrence risk λ_S as

$$\begin{aligned} \lambda_S &= K^{-1}P(D_2 = 1 \mid D_1 = 1, \text{sibs}) \\ &= K^{-2}P(D_1 = D_2 = 1 \mid \text{sibs}) \\ &= \prod_{\ell=1}^{m} \left(\frac{1 + e^{\beta_\ell}}{2}\right)^2 . \end{aligned} \qquad (5)$$

According to equation (5), the fractional contribution of the PAR gene (gene 1) to the recurrence risk λ_S is

$$F_{\text{PAR}} = \frac{[(1 + e^{\beta_1})/2]^2}{\lambda_S} . \qquad (6)$$

The parameter β_1 is estimable from IBD sharing data in affected sibs, because from equation (2) and Bayes's Rule the probability that two affected sibs share j alleles IBD at the PAR locus 1 is given by

$$z_j = \frac{\alpha_j e^{j\beta_1}}{\sum_{i=0}^{2} \alpha_i e^{i\beta_1}}, \; j = 0,1,2 . \qquad (7)$$

In this equation, $\alpha_0 = 1/4$, $\alpha_1 = 1/2$, and $\alpha_2 = 1/4$ are the Mendelian probabilities that the sibs share 0, 1, and 2 alleles IBD at the PAR locus. Thus, in principle, one could (1) estimate β_1 from linkage data in the PAR, (2) estimate the sibling recurrence risk from epidemiological data, and (3) combine these two estimates in equation (6) to attribute a fractional contribution F_{PAR} of hereditary Hodgkin disease to the putative PAR gene. For example, the estimate $\hat{\beta}_1 = .562$, obtained by Horwitz and Wiernik, gives $F_{\text{PAR}} = .01$, using the recurrence risk $\lambda_S = 210$ of Hafez et al. (1985), and it gives $F_{\text{PAR}} = .27$, using the value $\lambda_S = 7$ of Grufferman et al. (1977). When β_1 is close to zero, $[(1 + e^{\beta_1})/2]^2 \sim e^{\beta_1}$ and equation (6) becomes $F_{\text{PAR}} \sim \exp(\beta_1 - \ln\lambda_s)$. This approximation gives $F_{\text{PAR}} = .01$ for $\lambda_S = 210$ and $F_{\text{PAR}} = .25$ for $\lambda_S = 7$. (Inexplicably, Horwitz and Wiernik used the ratio $\hat{\beta}_1/\ln\lambda_S$ for the fraction of hereditary Hodgkin disease due to a gene in the PAR. Thus, with $\hat{\beta}_1 = .562$, they estimated this fraction as .11 for $\lambda_S = 210$ and as .29 for $\lambda_S = 7$.)

In practice, however, such attribution is inappropriate. It requires the assumption that IBD status at the PAR gene equals IBD status at the marker (which is an arbitrary sex-specific locus). In fact, the unknown genetic distance between marker and PAR gene and the unknown penetrance of the PAR gene (which determines β_1) are completely confounded: highly penetrant genes more distal from the marker will yield the same estimates $\hat{\beta}_1$ as less-penetrant genes close to the marker.

In summary, IBD status at the PAR gene cannot be inferred from sexual phenotypes of ASPs, and thus equation (7) cannot be used to estimate β_1. This also can be seen by considering the usual nonparametric ASP test, which evaluates the mean number of alleles shared at the marker. ASPs of the same sex share an average of 1.5 marker alleles IBD, whereas ASPs of the opposite sex share an average of 0.5 such alleles. Letting n denote the number of sex-concordant pairs among the 102 sib pairs described by Horwitz and Wiernik, the ASP test is based on the score $1.5n + 0.5(102 - n) = n +$ constant. The ASP test statistic is

$$T^2 = \frac{(n - 102p)^2}{102p(1 - p)} ,$$

where p denotes the null frequency of sex-concordant sib pairs. Using the estimate $P = (.593)^2 + (.407)^2 = .5173$, where .593 and .407 are the proportions of males and females, respectively, among the 204 sibs, we have $T^2 = 4.11$ for $n = 63$ sex-concordant pairs. This ASP test simply evaluates the statistical significance of the observed sex concordance among the 102 ASPs, allowing for excess Hodgkin disease risk in males. In conclusion, without genotype data for multiple markers in the p-terminal PAR, the only inferences possible are those concerning the magnitude of any excess sex concordance among ASPs; it is not possible to infer the location or relative importance of a PAR gene for Hodgkin disease.

These comments notwithstanding, we are grateful to the authors for their seminal and potentially important observations. Further progress in our understanding of the genetic etiology of Hodgkin disease clearly requires more detailed marker data among multiple-case families, both in the PAR and elsewhere in the genome.

Acknowledgments

This research was supported by National Institutes of Health grant R35 CA47448.

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Electronic-Database Information

The URL for data in this article is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Hodgkin disease [MIM 236000] and LWD [MIM 127300])

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0002-9297/2000/6702-0038$02.00

Am. J. Hum. Genet. 67:537, 2000

Reply to Whittemore and Shih

To the Editor:

We thank Whittemore and Shih for their thoughtful discussion of our paper and are indebted to them for detecting two errors in the estimate of the *P* value in gender skewing and the calculation of the component β. The former led us to underemphasize the significance of the gender skewing, whereas the latter approximation appears to have had little effect.

We agree that both the LOD-score method and the β analysis have failings, as discussed in our paper. Whittemore and Shih appropriately point out additional limitations. Parametric linkage analysis conceivably allows for θ to be determined as a function of gender skewing. For Leri-Weill dyschondrosteosis (LWD), where there is little evidence of genetic heterogeneity, the calculated relationship is likely to remain correct. The range of θ, however, is subject not only to errors from lack of appreciation of complexity, as Whittemore and Shih remind us, but also to genetic-model misspecification and, therefore, remains highly uncertain. It is worth noting that the largest sibships concordant for Hodgkin disease (HD) (i.e., those with four or five affected children, as shown in table 3 of our article) demonstrate the greatest sex concordance, supporting the assertion that, if there were to be an HD gene situated in the pseudoautosomal region (PAR), then it is rather more likely to be centromerically situated than what is suggested from the calculated θ of the complete data set (i.e., including table 2 of our article). The β analysis suffers from the inability to measure the genetic distance between the putative locus and the marker—here, phenotypic sex. Neither approach is ideal when the marker is nothing but the sex of the patient as reported in the literature.

We wish to continue to emphasize the speculative nature of the hypothesis that an HD gene resides in the PAR. This conjecture can only be validated by studies utilizing a distribution of molecular genetic markers within the PAR. Because the PAR can easily be overlooked in genomewide screens for linkage and because two lines of evidence, gender concordance and the unique family segregating both HD and LWD, lead to the suggestion of a PAR locus, we ask that this hypothesis not be overlooked should sufficient clinical samples ultimately become available to put it to the test.

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0002-9297/2000/6702-0039$02.00