tor signaling by a complex between a kinase and a phosphatase. J Exp Med 189:111–121
Fogdell-Hahn A, Ligers A, Gronning M, Hiller J, Olerup O (2000) Multiple sclerosis: a modifying influence of HLA class I genes in an HLA class II associated autoimmune disease. Tissue Antigens 55:140–148
Genain CP, Cannella B, Hauser SL, Raine CS (1999) Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med 5:170–175
Gjorloff-Wingren A, Saxena M, Williams S, Hammi D, Mustelin T (1999) Characterization of TCR-induced receptor-proximal signaling events negatively regulated by the protein tyrosine phosphatase PEP. Eur J Immunol 29:3845–3854
Gregorieff A, Cloutier JF, Veillette A (1998) Sequence requirements for association of protein-tyrosine phosphatase PEP with the Src homology 3 domain of inhibitory tyrosine protein kinase p50(csk). J Biol Chem 273:13217–13222
Haines JL, Ter-Minassian M, Bazyk A, Gusella JF, Kim DJ, Terwedow H, Pericak-Vance MA, et al (1996) A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. Nat Genet 13:469–471
Haines JL, Terwedow HA, Burgess K, Pericak-Vance MA, Rimmler JB, Martin ER, Oksenberg JR, Lincoln R, Zhang DY, Banatao DR, Gatto N, Goodkin DE, Hauser SL (1998) Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity. Hum Mol Genet 7:1229–1234
Hasegawa K, Martin F, Huang G, Tumas D, Diehl L, Chan AC (2004) PEST domain-enriched tyrosine phosphatase (PEP) regulation of effector/memory T cells. Science 303: 685–689
Hauser SL, Goodin D (2001) Multiple sclerosis and other demyelinating diseases. In: Braunwald E, Fauci AD, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's principle of internal medicine, 15th ed. McGraw Hill, New York, pp 2452–2461
Kyogoku C, Langefeld CD, Ortmann WA, Lee A, Selby S, Carlton VEH, Chang M, Ramos P, Baechler EC, Batliwalla FM, Novitzke J, Williams AH, Gillett C, Rodine P, Graham RR, Ardlie KG, Gaffney PM, Moser KL, Petri M, Begovich AB, Gregersen PK, Behrens TW (2004) Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. Am J Hum Genet 75:504–507
Lee AT, Li W, Liew A, Bombardier C, Weisman M, Massarotti EM, Kent J, Wolfe F, Begovich AB, Gregersen PK. The PTPN22 R620W polymorphism associates with RF positive rheumatoid arthritis in a dose-dependent manner but not with HLA-SE status. Genes Immun (in press)
Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H (2000) Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 47:707–717
Marrack P, Kappler J, Kotzin BL (2001) Autoimmune disease: why and where it occurs. Nat Med 7:899–905
Martin ER, Bass MP, Gilbert JR, Pericak-Vance MA, Hauser ER (2003) Genotype-based association test for general pedigrees: the genotype-PDT. Genet Epidemiol 25:203–213
Martin ER, Monks SA, Warren LL, Kaplan NL (2000) A test for linkage and association in general pedigrees: the pedigree disequilibrium test. Am J Hum Genet 67:146–154
O'Connell JR, Weeks DE (1998) PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet 63:259–266
Oksenberg JR, Barcellos LF, Cree BA, Baranzini SE, Bugawan TL, Khan O, Lincoln RR, Swerdlin A, Mignot E, Lin L, Goodin D, Erlich HA, Schmidt S, Thomson G, Reich DE, Pericak-Vance MA, Haines JL, Hauser SL (2004) Mapping multiple sclerosis susceptibility to the *HLA-DR* locus in African Americans. Am J Hum Genet 74:160–167
Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273:1516–1517
Rubio JP, Bahlo M, Butzkueven H, van der Mei IAF, Sale MM, Dickinson JL, Groom P, Johnson LJ, Simmons RD, Tait B, Varney M, Taylor B, Dwyer T, Williamson R, Gough NM, Kilpatrick TJ, Speed TP, Foote SJ (2002) Genetic dissection of the human leukocyte antigen region by use of haplotypes of Tasmanians with multiple sclerosis. Am J Hum Genet 70: 1125–1137
Sawcer S, Jones HB, Feakes R, Gray J, Smaldon N, Chataway J, Robertson N, Clayton D, Goodfellow PN, Compston A (1996) A genome screen in multiple sclerosis reveals susceptibility loci on chromosomes 6p21 and 17q22. Nat Genet 13:464–468
Wandstrat A, Wakeland E (2001) The genetics of complex autoimmune diseases: non-MHC susceptibility genes. Nat Immunol 2:802–809

Address for correspondence and reprints: Dr. Ann B. Begovich, Celera Diagnostics, 1401 Harbor Bay Parkway, Alameda, CA 94502. E-mail: Ann.Begovich@celeradiagnostics.com

0002-9297/2005/7601-0020$15.00

Am. J. Hum. Genet. 76:187–189, 2005

Corrections to the Parameterization of Constraints on Allele Sharing in Sibling Pairs Alter Covariate-Parameter Estimates but Not Sharing-Probability Estimates or Power of Tests for Linkage

To the Editor:

Errors in appendix B of our 1999 article in the *Journal* (Greenwood and Bull 1999) were recently pointed out to us (D. Weeks and H.-J. Tsai, personal communication). The simultaneous-boundary–constrained estimates for $z_0(x_i)$ presented in 1999 do not give the correct values for the covariate parameters under the null hypothesis. The correct expression for the expected proportion of sibling pairs sharing zero alleles identical by

Table 1

Original and Corrected Results of Simulation Models

Model, Constraint Method, and Covariate(s)	df	Results Reported in 1999		Corrected Results	
		Mean LOD Score	5% Empirical Power	Mean LOD Score	5% Empirical Power
Single-gene model (model 1; original table 2)[a]:					
Unconstrained model:					
No covariates	2	2.20	.70	2.19	.67
Constrained model:					
No covariates, no dominance variance	1	1.97	.74	1.96	.73
No covariates, no additive variance	1	1.26	.53	1.25	.53
No covariates, minmax-optimal constraint	1	1.78	.71	1.77	.71
Mean age at onset, no dominance variance, simultaneous-boundary constraint	2	3.08	.87	3.08	.85
Mean age at onset, no additive variance, simultaneous-boundary constraint	2	1.88	.58	1.88	.54
Mean age at onset, minmax-optimal simultaneous-boundary constraint	2	2.61	.82	2.80	.77
Gene-environment–interaction model (model 2b; original table 3)[b]:					
Unconstrained model:					
No covariates	2	1.47	.42	1.50	.44
Constrained model:					
No covariates, minmax-optimal constraint	1	1.23	.54	1.24	.51
Two covariates, minmax-optimal simultaneous-boundary constraint	2	1.72	.44	1.78	.41

[a] For the single-gene model, 34/500 linked data sets were excluded from the results in the 1999 article (Greenwood and Bull 1999) because of lack of convergence. After correction, no data sets were excluded.

[b] For the gene-environment–interaction model, 82/500 data sets were excluded from the results in the 1999 article (Greenwood and Bull 1999) because of lack of convergence. After correction, 13/500 data sets were excluded.

descent (IBD) under the simultaneous-boundary constraint with no additive variance should be

$$z_0(x_i) = \frac{\exp(\beta_0' x_i)}{1 + 3\exp(\beta_0' x_i)} .$$

The relationships between this proportion and those for sharing one or two alleles IBD do not change from the 1999 article: $z_1(x_i) = 2z_0(x_i)$ and $z_2(x_i) = 1 - 3z_0(x_i)$.

For the minmax-optimal simultaneous-boundary constraint, the correct expression should be

$$z_0(x_i) = \frac{0.645\exp(\beta_0' x_i)}{1 + 1.58\exp(\beta_0' x_i)} .$$

As in the 1999 article, the constraints on the other sharing proportions are $z_1(x_i) = 0.355 + 0.58z_0(x_i)$ and $z_2(x_i) = 0.645 - 1.58z_0(x_i)$. Note that both the original (see appendix B in Greenwood and Bull 1999) and the corrected expressions for $z_0(x_i)$ satisfy the specified constraints on the expected sharing proportion $z_j(x_i)$ and differ only in those values of the covariate-associated parameter vector β_0 that correspond to specific null or alternative hypotheses.

When written in terms of the sharing proportion $z_0(x_i)$, the score equations—based on the LOD$^{**}(\beta_0)$ expressions given in appendix B (Greenwood and Bull 1999) and used in the M step of the estimation algorithm—are identical for the original and corrected expressions. Provided that the z_{ij}s in the E step are updated using the $z_0(x_i)$ estimates, the final $z_0(x_i)$ estimates from the expectation-maximization algorithm, and hence the LOD scores for the test of linkage with covariates, will also be identical.

This can be considered as a special case of the invariance of the likelihood to reparameterization. Therefore, the original conclusions concerning relative power and effects of constraints are unchanged.

We have rerun our simulations to confirm these theoretical conclusions, and we show here in table 1 some corrected results and original results from tables 2 and 3 of the 1999 article (Greenwood and Bull 1999). The corrected algorithms almost always converge, whereas we previously had more difficulty in obtaining convergence with these two constraint methods. Thus, we conclude that the small differences in mean LOD scores or in significance levels are a result of the fact that we no longer had to exclude as many data sets from our summaries. Therefore, although estimates of the parameter β_0 would not be correct if the expressions in the 1999 article were used, our conclusions about the power of the various approaches have not changed.

Celia M. T. Greenwood[1,2] and Shelley B. Bull[2,3]
[1]*Program in Genetics and Genomic Biology, Hospital for Sick Children,* [2]*Department of Public Health Sciences, University of Toronto, and* [3]*Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto*

Reference

Greenwood CMT, Bull SB (1999) Analysis of affected sib pairs, with covariates—with and without constraints. Am J Hum Genet 64:871–885

Address for correspondence and reprints: Dr. Celia M. T. Greenwood, Genetics and Genomic Biology, Elm 11-101, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. E-mail: celia.greenwood@utoronto.ca

0002-9297/2005/7601-0021$15.00