Letters to the Editor

Am. J. Hum. Genet. 72:496, 2003

Simulation-Based *P* Values: Response to North et al.

To the Editor:

North et al. (2002) discussed the estimation of a *P* value on the basis of computer (i.e., Monte Carlo) simulations. They emphasized that such a *P* value is an estimate of the true *P* value. This is essentially their only point with which we agree. The letter from North et al. is more likely to confuse than enlighten.

Consider an observed test statistic, x, that under the null hypothesis follows some distribution, f. Let X be a random variable following the distribution f. We seek to estimate the *P* value, $p = \Pr(X \geq x)$. Let $y_1, \ldots, y_n$ be independent draws from f, obtained by computer simulation. Let $r = \#\{i : y_i \geq x\}$ (i.e., the number of simulated statistics greater than or equal to the observed statistic). Let $\hat{p} = r/n$ and $\tilde{p} = (r + 1)/(n + 1)$.

North et al. (2002) stated that $\hat{p}$ is "not strictly correct" and that $\tilde{p}$ is "the most accurate estimate of the *P* value." They further called $\tilde{p}$ "the true *P* value."

We strongly disagree with this characterization. First, minor differences in *P*-value estimates on the order of Monte Carlo error should not be treated differently in practice, and so it is immaterial whether one uses $\hat{p}$ or $\tilde{p}$. Second, $\hat{p}$ is a perfectly reasonable estimate of p. Indeed, in many ways $\hat{p}$ is superior to $\tilde{p}$. Given the observed test statistic, x, r follows a binomial (n,p) distribution, and so $\hat{p}$ is unbiased, whereas $\tilde{p}$ is biased. (The bias of $\tilde{p}$ is $(1 - p)/(n + 1)$.) Further, $\hat{p}$ has smaller mean square error (MSE) than $\tilde{p}$, provided that $p < n/(1 + 3n) \approx 1/3$. (The MSE of $\hat{p}$ is $p(1 - p)/n$, whereas that of $\tilde{p}$ is $(1 - p)(np + 1 - p)/(n + 1)^2$.)

These results are contrary to those of North et al. (2002) because they evaluate the performance of $\tilde{p}$ under the joint distribution of both the observed and Monte Carlo data, whereas we prefer to condition on the observed value of the test statistic. Evaluating *P*-value estimates conditionally on the observed data is widely accepted when the estimation is performed via analytic approximations.

Regarding the question of how many simulation replicates to perform, we recommend consideration of the precision of the estimate, $\hat{p}$, using the properties of the binomial distribution, rather than adherence to a rule such as $r \geq 10$. Standard statistical packages, such as R (Ihaka and Gentleman 1996), allow one to calculate a CI for the true *P* value and to perform a statistical test, such as whether the true *P* value is <.01.

KARL W. BROMAN AND BRIAN S. CAFFO
Department of Biostatistics
Johns Hopkins University
Baltimore

References

Ihaka R, Gentleman R (1996) R: a language for data analysis and graphics. J Comp Graph Stat 5:299–314

North BV, Curtis D, Sham PC (2002) A note on the calculation of empirical *P* values from Monte Carlo procedures. Am J Hum Genet 71:439–441

Address for correspondence and reprints: Dr. Karl W. Broman, Department of Biostatistics, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205. E-mail: kbroman@jhsph.edu

0002-9297/2003/7202-0032$15.00

Am. J. Hum. Genet. 72:496–498, 2003

On Estimating *P* Values by Monte Carlo Methods

To the Editor:

North et al. (2002) propose a new formula for the empirical estimation of *P* values by Monte Carlo methods to replace a standard conventional estimator. They claim that their new formula is "correct" and "most accurate" and that the conventional formula is "not strictly correct," repeating this claim many times in their letter. The claim, however, is incorrect, and the conventional formula is the correct one.

The North et al. claim arises when a test statistic (called here "t") takes a certain numerical value (called here "t^*") when calculated from data from some experiment, and it is required to find an unbiased estimate of the *P* value corresponding to t^* by Monte Carlo simulation. This is done by performing n Monte Carlo simulations, all performed under the null hypothesis tested

in the original experiment and with the same sample size and other characteristics as for the original experiment. Suppose, to be concrete, that sufficiently large positive values of the test statistic t are significant. Then, we define "r" as the number of simulations in which the simulation value of t is greater than or equal to the observed value t^*. North et al. claim that an unbiased, and thus preferred, estimate of the P value arising from these simulations is $(r + 1)/(n + 1)$ instead of the conventional estimate r/n. This claim is incorrect.

Strangely, North et al. (2002) themselves show by algebra that the mean value of their estimator $(r + 1)/(n + 1)$ is $(nP + 1)/(n + 1)$, where "P" is the P value to be estimated. Since this is not equal to P, their P value estimator is biased. Further, their calculation also shows that the mean value of the conventional estimator r/n, whose use they do not recommend, is the desired value P. Thus, the conventional estimator is unbiased. Thus, there is an internal inconsistency in their argument, and their algebraic calculations contradict their claim and the argument leading to it. The algebraic calculations are correct. It is important to see why the argument given in North et al. (2002) is incorrect, since the reasoning involved relates to the theory and practice of Monte Carlo simulation procedures that are performed increasingly in genetics, in particular to questions surrounding P values and type 1 errors.

The incorrect argument given by North et al. (2002) is that if the original data were generated under the null hypothesis tested, then, in all, $n + 1$ "experiments" were conducted, of which one is real and n simulation. With r as defined above, in $r + 1$ of these, the value of the statistic t is either equal to the observed value t^* or is greater than this value. It is then claimed that the estimator $(r + 1)/(n + 1)$ is an unbiased estimator of the null hypothesis probability that the test statistic t exceeds t^* when the null hypothesis is true.

The error in this argument is, perhaps, best demonstrated by considering parallel reasoning used in the genetic ascertainment sampling context, exemplified as follows. Suppose that we wish to estimate the proportion of girls in a population, using a sample of families from that population. However, the sampling procedure is such that only families in which the oldest child is a girl are included in the sample. Clearly, using all children in the sample to estimate the proportion of girls in the population is incorrect, and the sample proportion of girls will overestimate the population proportion. The oldest child in each family, automatically included in the category of interest (girls), must be excluded in the estimation process. The analogy with the Monte Carlo case is that the observed value of the test statistic found from the actual data must be excluded in estimating a P value, since it is similarly automatically included in the category of interest (greater than or equal to itself). Any mathematical calculation concerning P values that does take this into account will be incorrect.

It now appears that North et al. (2002) used mistaken terminology, and that the claim that they wished to make does not concern P value estimation, but that use of $(r + 1)/(n + 1)$ "provides the correct type 1 error rate." More precisely, if the type 1 error is chosen to be α, then it is claimed that rejecting the null hypothesis when $(r + 1)/(n + 1) < \alpha$ leads to the desired type 1 error of 5%.

To see this in formal statistical terms, the null hypothesis is rejected, with the notation and assumptions given above, if the value of r is "too low." More specifically, with the chosen type 1 error of α, the null hypothesis is rejected if $r < K$, where K is chosen so that Prob($r < K$, given null hypothesis is true) $= \alpha$.

The one "experimental" and n simulation values of t, leading to a total of $n + 1$ values, can be listed in ascending order. The event that $r < K$ is identical to the event that the experimental value of t lies among the highest $K + 1$ of these $n + 1$ values. The null hypothesis probability of this is $(K + 1)/(n + 1)$. Equating the probability$(K + 1)/(n + 1)$ with α, we get $K = (n + 1)\alpha - 1$ $K = (n + 1)\alpha - 1$. The event $r < K$ is, thus, the same as the event $(r + 1)/(n + 1) < \alpha$, and this is the criterion that North et al. give.

This procedure does not, however, imply, as claimed by North et al. (2002), that $(r + 1)/(n + 1)$ is an unbiased estimate of the P value. It is best to keep the questions of unbiased estimation of the P value and the nature of the testing procedure that leads to a desired type 1 error separate. Pursuing this point, it is not clear in what sense North et al. relate, as they do, a P value estimate to a type 1 error. They claim, for example, that when $r = 0$, so that the standard procedure P value estimate r/n is also 0, it is implied, under the standard procedure, that the type 1 error is also 0. This claim is incorrect. A type 1 error in statistics is set in advance, typically 5% or 1%, and the value so chosen for it is not in any way determined by or estimated from the observed value of any statistic.

Warren J. Ewens

Department of Biology
University of Pennsylvania
Philadelphia

References

North BV, Curtis D, Sham PC (2002) A note on the calculation of empirical P values from Monte Carlo procedures. Am J Hum Genet 71:439–441

Address for correspondence and reprints: Dr. Warren J. Ewens, Department of Biology, University of Pennsylvania, Philadelphia, PA 19104-6018. E-mail: wewens@sas.upenn.edu

0002-9297/2003/7202-0033$15.00

Am. J. Hum. Genet. 72:498–499, 2003

A Note on the Calculation of Empirical *P* Values from Monte Carlo Procedures

To the Editor:

We welcome the opportunity to correct our mistaken terminology in referring to $(r + 1)/(n + 1)$ as an unbiased estimate of P, where a Monte Carlo procedure has been carried out with n simulations, of which r exceed the observed statistic obtained from the real data set. As we ourselves pointed out (North et al. 2002), this estimate is indeed slightly biased. What we intended to write was that using this estimate is valid in the sense that it produces the correct type 1 error rate. According to Cox and Hinkley (1974), the observed P value of a study, denoted as P_{obs}, is defined as $\Pr(T \geqslant t_{obs}; H_0)$, the probability that the test statistic T is greater than or equal to its actual value t_{obs} from the observed data, if the null hypothesis, H_0, is true. Their interpretation of the P value is that it is "the probability that we would mistakenly declare there to be evidence against H_0, were we to regard the data under analysis as just decisive against H_0." Since $P \leqslant P_{obs}$ if and only if $T \geqslant t_{obs}$, it follows that $\Pr(T \geqslant t_{obs}; H_0) = \Pr(P \leqslant P_{obs}; H_0) = P_{obs}$. In other words, we should obtain a P value of .05 (or lower) with frequency 0.05, and a P value of .01 (or lower) with frequency 0.01, and so on, if the null hypothesis is true. If a test procedure produces P values of .05 (or lower) with greater frequency than 0.05, when the null hypothesis is true, then the procedure is anticonservative.

Our article (North et al. 2002) was motivated by the recognition that the common practice of using r/n as the P value from a Monte Carlo procedure is, in fact, anticonservative, whereas the use of $(r + 1)/(n + 1)$ provides the correct type 1 error rate. There is nothing novel about the use of $(r + 1)/(n + 1)$—it is published in a standard textbook on Monte Carlo methods (Davison and Hinkley 1997), and we merely sought to give it greater prominence and to investigate its implications. We accept that it is mildly counterintuitive, and so some people may find the reasons for its usage difficult to grasp. Nevertheless, we remain convinced that it is far preferable to use an estimate that is slightly biased but yields the correct type 1 error rate than one that is unbiased but is demonstrably anticonservative.

One way to understand the justification for using $(r + 1)/(n + 1)$ rather than r/n is as follows. When the null hypothesis is true, the actual value of the test statistic and the n replicate values based on simulations constitute $n + 1$ independent realizations of the same random variable. All possible ranks of the actual test statistic among these $n + 1$ values, from rank 1 to rank $n + 1$ in descending order of magnitude, are, therefore, equally probable. The probability of the actual test statistic being exceeded in exactly r of n simulated replicates (i.e., of being ranked $r + 1$) is, therefore, $1/(n + 1)$. Likewise, the probability of the actual test statistic being exceeded in r or fewer of n simulated replicates (i.e., of being ranked $r + 1$ or higher) is $(r + 1)/(n + 1)$.

For those who are not convinced by the above argument, we present a more mathematical derivation. The probability that the actual test statistic is exceeded in exactly r simulations, conditional on any particular value of P, is given by the binomial distribution with parameters n and P. The unconditional probability that the actual test statistic is exceeded in exactly r simulations is obtained by integrating the product of this conditional probability and the density function $f(P)$ of P, over the possible range of P. Therefore,

$$\begin{aligned}\Pr(r; \mathrm{H}_0) &= \int_0^1 \frac{n!}{(n-r)!r!} p^r (1-p)^{n-r} \mathrm{f}(p)\mathrm{d}p \\ &= \frac{n!}{(n-r)!r!} \int_0^1 p^r (1-p)^{n-r}\,\mathrm{d}p \\ &= \frac{n!}{(n-r)!r!} \frac{(n-r)!r!}{(n+1)!} \\ &= \frac{1}{n+1}\end{aligned}$$

for $r = 0,1,\ldots,n$. The second step in the derivation depends on the density function of P being uniform in [0,1] under the null hypothesis, whereas the third step is due to the recognition that the integral is a beta function with parameters $n - r + 1$ and $r + 1$. From the fact that the probability of achieving any particular value of r is $1/(n + 1)$, it follows that the probability of the actual test statistic being exceeded in r or fewer of n simulated replicates (i.e., of being ranked $r + 1$ or higher) is $(r + 1)/(n + 1)$.

For anyone who continues to remain skeptical in spite of these theoretical arguments, it is trivial to carry out simulation procedures that demonstrate that using r/n is anticonservative, whereas using $(r + 1)/(n + 1)$ does indeed yield the correct type 1 error rate. Anybody who

takes the trouble to do this cannot fail to discover this for himself. For example, here is a simple C program that demonstrates the phenomenon:

```
#include <stdio.h>
#include <stdlib.h>
float p1,p2,m1,m2,r,alpha=0.01;
int x,j,n=500;
long i,nsim=1000000;
int main(int argc, char *argv[])
{
for (i=0;i<nsim;++i)
{
x=rand();
for (r=0,j=0;j<n;++j)
   if (rand()>=x) ++r;
if (r/n<=alpha) ++m1;
if ((r+1)/(n+1)<=alpha) ++m2;
}
printf("Using r/n, Type 1 error =
   %f\n",m1/nsim);
printf("Using (r+1)/(n+1), Type 1 error =
   %f\n",m2/nsim);
}
```

As the theory predicts, when the number of simulations is 500, using r/n and $(r + 1)/(n + 1)$ provide an empirical P value of .01 (or lower) with frequency 0.012 and 0.010, respectively. One can readily use a range of different values to see that the argument holds in all situations.

Although lack of bias is desirable, it is not so crucial a property as that of providing the correct type 1 error interpretation. The estimator r/n is unbiased but anticonservative, and its usage can lead, for example, to the absurd assertion that when $r = 0$, then the type 1 error rate is 0, implying that the results are impossible under the null hypothesis and, therefore, must be rejected. Because r/n and $(r + 1)/(n + 1)$ are both linear functions of r, they are perfectly correlated with each other. Using $(r + 1)/(n + 1)$ introduces only a small bias, being $(1 - p)/(n + 1)$, which diminishes with increasing n. Proponents of using r/n might argue that it should be regarded merely as an estimate of the true P value, and not as an empirical P value. In our view, this is unnecessarily cumbersome, since $(r + 1)/(n + 1)$ *can* be interpreted directly as an empirical P value, which will have the correct type 1 error rate.

B. V. North,[1] D. Curtis,[1] and P. C. Sham[2]
[1]*Academic Department of Psychiatry, St. Bartholomew's and Royal London School of Medicine and Dentistry, and* [2]*Department of Psychological Medicine, Institute of Psychiatry, London*

References

Cox DR, Hinkley DV (1974) Theoretical statistics. Chapman and Hall, London

Davison AC, Hinkley DV (1997) Bootstrap methods and their application. Cambridge University Press, Cambridge

North BV, Curtis D, Sham PC (2002) A note on the calculation of empirical *P* values from Monte Carlo procedures. Am J Hum Genet 71:439–441

Address for correspondence and reprints: Dr. D. Curtis, Department of Adult Psychiatry, Royal London Hospital, London E1 1BB, United Kingdom. E-mail: dcurtis@hgmp.mrc.ac.uk

0002-9297/2003/7202-0034$15.00

Am. J. Hum. Genet. 72:499–502, 2003

Confirmatory Evidence for Linkage of Relative Hand Skill to 2p12-q11

To the Editor:

We previously reported in the *Journal* the first genomewide linkage screen for a measure related to handedness in humans (Francks et al. 2002), in which we found evidence for a quantitative trait locus (QTL) influencing relative hand skill on chromosome 2p12-q11 (P = .00007). The screen was performed using 195 reading-disabled (RD) sibling pairs (Fisher et al. 2002), although reading ability was apparently unrelated to handedness in this sample. The 2p12-q11 linkage was the most significant in the screen by 1.5 orders of magnitude and approached the threshold for genomewide significance proposed by Lander and Kruglyak (1995) (threshold P = .00002). However, we failed to replicate the QTL in a second sample of a similar composition (143 sibling pairs). Therefore, the possibility remained that this was a false positive result, brought about by multiple testing of markers across the entire genome.

Now, we have found further evidence for the 2p12-q11 QTL in a new sample of 105 pairs of adult brothers drawn from a sample of 168 unrelated male sibships (338 brothers) that was originally collected for investigating X-linked effects on handedness (described by Laval et al. [1998]). As before, we assessed relative hand skill using the test of Annett (1985), which involves measuring the time taken to move, with each hand, a row of pegs from one set of slots on a board to another. A relative hand skill quotient, PegQ, was derived for each subject as $(L - R)/[(L + R)/2]$; that is, the difference between left and right hand times, adjusted for overall hand skill (fig. 1*a*).

The recruitment criterion that all brothers in each sib-

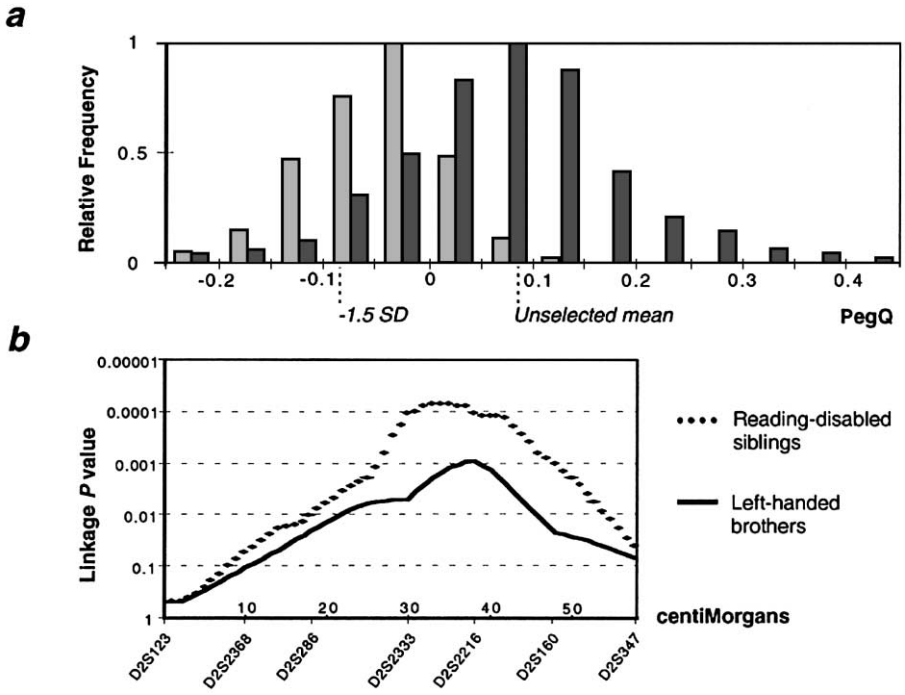

Figure 1 *a*, PegQ distribution in 222 siblings with RD who appeared normal for this measure and were previously analyzed genomewide for linkage (*black*) and in 338 left-writing-handed brothers from whom the current study sample was drawn (*gray*). Positive scores indicate superior relative right hand skill; the positive mean in the reading-disabled siblings is characteristic of unselected populations, whereas the sample of left-handed writers had a negative mean. We selected as extreme left-handed "probands" those individuals whose PegQ scores were >1.5 SD below the normal population mean. *b*, Comparison of linkage to PegQ across 2p16-q14 in RD siblings (Francks et al. 2002) and the left-handed brothers of the present study. *X*-axis, genomic interval with markers shown; *Y*-axis, pointwise significance of linkage.

ship should write with their left hands constituted a form of imperfect phenotypic selection for PegQ. This resulted in curtailed PegQ variance in the 338 brothers (fig. 1*a*) and suggested that quantitative linkage analysis of the whole sample might be underpowered. We therefore selected sibships on the basis of their suitability for linkage analysis with basic DeFries-Fulker regression (Fulker et al. 1991), which can derive power from extreme phenotypic selection. Extreme left handed "probands" were designated as scoring below −1.5 SD (fig. 1*a*), relative to the sample of reading-disabled siblings (who scored as an unselected population for relative hand skill). This yielded 101 probands in 88 independent sibships. The threshold of −1.5 SD was chosen to balance increased power from increasing severity of selection against diminishing power because of reduced sample size. No other threshold scores for designating probands were used.

We genotyped the 88 sibships at seven microsatellite markers spanning 2p16-q14 and obtained multipoint identity-by-descent (IBD) sharing information across this interval, using the software Genehunter 2.1 (Pratt et al. 2000). Allele frequencies were calculated using data from all parents plus one random sibling in each family, and the genetic marker map was the same as used by Francks et al. (2002) (see fig. 1*b*). We then assessed the regression of PegQ in brothers of extreme left-handers toward the population mean, as a function of proband scores and IBD sharing with probands, using basic DeFries-Fulker regression as implemented in SAS macros by Lessem and Cherny (2001). A double entry procedure was used when a sibship contained more than one proband, as recommended (Fulker et al. 1991). This yielded a total of 91 independent proband-cosib pairs and 105 total proband-cosib pairs. Unbiased pointwise empirical significance levels for multipoint linkage results were obtained by performing 100,000 genotype simulations while fixing the family structures and phenotypes of the real sample (as described by Francks et al. [2002] and Fisher et al. [2002]) and then analyzing these replicates for linkage.

The peak linkage *t* score was −3.51 (fig. 1*b*), asymptotic pointwise $P = .00035$, empirical pointwise $P = .00090$, thus greatly exceeding significance guidelines for confirmation of linkage (guideline $P = .01$; Lander and Kruglyak [1995]). The new linkage curve was strikingly similar to that found in the genomewide screen, and this

concordance provides confirmatory evidence for the QTL over and above the significance level of the linkage (fig. 1*b*).

This linkage evidence confirms that, although handedness variation may be etiologically complex, there is at least one polymorphic genetic influence that is located on 2p12-q11. Epidemiological studies of twins have provided ambiguous data that point either to weak or else to nonsignificant genetic effects on handedness (Bishop 2001), but no large-scale twin studies have used the greater potential power inherent in a continuous description of the trait, whereas PegQ has shown familialities of up to 35% in our samples (Francks et al. 2002). Linkage analysis of handedness as a dichotomous trait is, therefore, likely to be underpowered, but only one study has so far attempted this approach, and for only six genomic regions (not including 2p12-q11), without identifying suggestive or significant linkage (Van Agtmael et al. 2002). Sex-dependent effects on cerebral lateralization and on the inheritance of handedness have pointed to the involvement of an X-linked genetic effect on handedness (Corballis et al. 1996; McKeever 2000), and suggestive or weak evidence for linkage of relative hand skill to a locus on Xq21 has been identified in both our RD siblings and the left-handed brothers (Laval et al. 1998; Francks et al. 2002), although Crow (2002) has suggested that any X-linked effect may be mediated by an epigenetic mechanism.

Roughly 90% of individuals perform complex manual tasks preferentially with their right hands, whereas slightly <10% are left-handed, and a small proportion are ambidextrous (McManus and Bryden 1992). No other primates show a population-level bias in handedness, and individual differences in human handedness are correlated with cerebral hemispheric asymmetries that underlie much complex human cognition, including language (McGrew and Marchant 1997; Geschwind et al. 2002), as well as with asymmetries of the motor cortex (Amunts et al. 1996). We predict that genes containing variants that influence handedness have an important role in the development of cerebral lateralization and may have been involved in the evolution of complex human cognition.

Acknowledgments

Many thanks to all of the left-handed brothers. We thank Timothy J. Crow for his involvement in this work. This research was funded by the Wellcome Trust and SANE (Schizophrenia—A National Emergency). S.E.F. is a Royal Society Research Fellow. A.P.M. is a Wellcome Principal Research Fellow.

Clyde Francks,[1] Lynn E. DeLisi,[4] Simon E. Fisher,[1] Steve H. Laval,[5] Judith E. Rue,[3] John F. Stein,[2] and Anthony P. Monaco[1]

[1]*Wellcome Trust Centre for Human Genetics,* [2]*Department of Physiology, University of Oxford, and* [3]*Research Institute, Churchill Hospital, Oxford;* [4]*Department of Psychiatry, New York University, New York; and* [5]*School of Biochemistry and Genetics, University of Newcastle, Newcastle-upon-Tyne*

References

Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K (1996) Asymmetry in the human motor cortex and handedness. Neuroimage 4:216–222

Annett M (1985) Left, right, hand and brain: the right shift theory. Laurence Erlbaum Associates, London

Bishop DV (2001) Individual differences in handedness and specific speech and language impairment: evidence against a genetic link. Behav Genet 31:339–335

Corballis MC, Lee K, McManus IC, Crow TJ (1996) Location of the handedness gene on the X and Y chromosomes. Am J Med Genet 67:50–52

Crow TJ (2002) Handedness, language lateralisation and anatomical asymmetry: relevance of protocadherin XY to hominid speciation and the aetiology of psychosis. Brit J Psychiat 181:295–297

Fisher SE, Francks C, Marlow AJ, MacPhie IL, Newbury DF, Cardon LR, Ishikawa-Brush Y, Richardson AJ, Talcott JB, Gayán J, Olson RK, Pennington BF, Smith SD, DeFries JC, Stein JF, Monaco AP (2002) Independent genome-wide scans identify a chromosome 18 quantitative-trait locus influencing dyslexia. Nat Genet 30:86–91

Francks C, Fisher SE, MacPhie IL, Richardson AJ, Marlow AJ, Stein JF, Monaco AP (2002) A genomewide linkage screen for relative hand skill in sibling pairs. Am J Hum Genet 70:800–805 (erratum 70:1075)

Fulker DW, Cardon LR, DeFries JC, Kimberling WJ, Pennington BF, Smith SD (1991) In: Pennington BF (Ed.) Reading disabilities: genetic and neurological influences. Kluwer, Dordrecht

Geschwind DH, Miller BL, DeCarli C, Carmelli D (2002) Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. Proc Natl Acad Sci 99:3176–3181

Lander E, Kruglyak L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247

Laval SH, Dann JC, Butler RJ, Loftus J, Rue J, Leask SJ, Bass N, Comazzi M, Vita A, Nanko S, Shaw S, Peterson P, Shields G, Smith AB, Stewart J, DeLisi LE, Crow TJ (1998) Evidence for linkage to psychosis and cerebral asymmetry (relative hand skill) on the X chromosome. Am J Med Genet 81:420–427

Lessem JM, Cherny SC (2001) DeFries-Fulker multiple regression of sibship QTL data: a SAS macro. Bioinformatics 17:371–372

McGrew WC, Marchant LF (1997) On the other hand: current

issues in and meta-analysis of the behavioural laterality of hand function in non-human primates. Yearb Phys Anthropol 40:201–232

McKeever WF (2000) A new family handedness sample with findings consistent with X-linked transmission. Br J Psychol 91:21–39

McManus IC, Bryden MP (1992) The genetics of handedness, cerebral dominance and lateralization. In: Rapin I, Segalowitz SJ (eds) Handbook of neuropsychology. Elsevier, Amsterdam

Pratt SC, Daly MJ, Kruglyak L (2000) Exact multipoint quantitative-trait linkage analysis in pedigrees by variance components. Am J Hum Genet 66:1153–1157

Van Agtmael T, Forrest SM, Williamson R (2002) Parametric and non-parametric linkage analysis of several candidate regions for genes for human handedness. Eur J Hum Genet 10:623–630

Address for correspondence and reprints: Dr. Anthony P. Monaco, Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford, UK, OX3 7BN. E-mail: anthony.monaco@well.ox.ac.uk

0002-9297/2003/7202-0035$15.00