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*Brief Research Communication*

# Location of the Handedness Gene on the X and Y Chromosomes

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**Accumulated data from five handedness surveys show that concordance for sex is slightly but reliably higher among siblings of the same handedness than among those of opposite handedness. This is consistent with Crow's theory that the genetic locus for handedness is in an X-Y homologous region of the sex chromosomes. The small size of the effect is predicted from genetic models in which there is a substantial random component underlying phenotypic left handedness. The findings are relevant to the putative role of cerebral asymmetry in the aetiology of psychosis.** © 1996 Wiley-Liss, Inc.

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In discussing anomalies of brain asymmetry in schizophrenia Crow has argued that a gene for asymmetry is located in an homologous region of the X and Y chromosomes either within [Crow, 1990a,b] or outside [Crow, 1993a,b] the exchange (pseudo-autosomal) region. There is also evidence that psychotic disorders might be associated with deviations from the normal pattern of right handedness [Green et al., 1989] and left-cerebral dominance [Crow, 1990a]. This raises the possibility that handedness, cerebral asymmetry, and psychotic disorder may depend, at least in part, on the same genetic locus.

If this locus is indeed on the sex chromosomes, then a male carrying a particular allele only on his X chromosome would pass it only to his daughters, while if he carried it only on his Y chromosome he would pass it only to his sons. Overall, then, the ratio of same-sex (SS) to opposite-sex (OS) siblings should exceed unity for those of like handedness, but be less than unity for those of opposite handedness. These effects are likely to be very small, since homozygotes would pass the allele to both sons and daughters, and females with a single copy could pass it to either. Moreover, recent single-gene models [Annett, 1985; McManus, 1985] of handedness propose that, where one allele (D for dextral) disposes toward right-handedness, the other (C for chance) disposes toward fluctuating asymmetry rather than left-handedness per se.

The concordance between the handedness and sex of sibling pairs can be measured by the fourfold point correlation, $\phi$, derived from the two-by-two table of same and opposite sex against same and opposite handedness. The OS/SS ratios and values of $\phi$ predicted by the single-gene models of McManus [1985] and Annett [1985] are shown in Table I. To test such predictions with acceptable power would require a sample of sibling pairs in excess of 12,000.

We have accumulated an effective sample of 14,500 sibling pairs from 1) two surveys at Cambridge University by McManus, one of undergraduates and the other of graduands and their parents [McManus, 1979]; 2) the British National Childhood Encephalopathy Study, in which parents of normal children matched to encephalopathy cases were surveyed [Madge et al., 1993]; 3) a survey of students at the University of Auckland and personal acquaintances of one of the authors (K.L.) and an appeal through a New Zealand national woman's magazine and an Auckland, New Zealand talkback radio show; and 4) a survey in British Columbia by Coren and Porac [1980]. In the first four, information was obtained on handedness of siblings and parents, and in some cases of grandparents, while the Canadian sample included information only on sibling pairs. Each survey was conducted as a study of the inheritance of handedness, without particular interest or emphasis on siblings per se. Handedness was assessed by slightly different questionnaires in the different surveys either in terms of a laterality index, in which left-handedness was defined as less than or equal to zero, or in terms of the writing hand. Ambidexterity was pooled with left-handedness. The numbers of respondents in each survey are given in Table II. With corrected values there was a total of 14,755.2 pairs of siblings made up

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TABLE I. Predictions of SS/OS Ratios, Four-Fold Point Correlations ($\phi$), and Critical Sample Sizes (N), According to Two Single-Gene Models of Handedness*

| Parental phenotypes (Mother × Father) | Offspring phenotypes R × R | R × L | L × L | $\phi$ | N |
|---|---|---|---|---|---|
| McManus's model | | | | | |
| R × R | 1.008 | 0.874 | 1.982 | 0.0222 | 15,928 |
| R × L | 1.039 | 0.826 | 2.176 | 0.0590 | 2,255 |
| L × R | 1.010 | 0.953 | 1.206 | 0.0148 | 35,838 |
| L × L | 1.053 | 0.877 | 1.356 | 0.0538 | 2,712 |
| Overall | 1.013 | 0.872 | 1.562 | 0.0246 | 12,972 |
| Annett's model | | | | | |
| R × R | 1.010 | 0.904 | 1.687 | 0.0224 | 15,645 |
| R × L | 1.008 | 0.956 | 1.166 | 0.0133 | 44,378 |
| L × R | 1.026 | 0.869 | 1.631 | 0.0415 | 4,558 |
| L × L | 1.024 | 0.935 | 1.158 | 0.0263 | 11,349 |
| Overall | 1.016 | 0.898 | 1.535 | 0.0234 | 14,336 |

*The parameters used to derive these predictions were: for McManus's model [1985], p(R/DD) = 1, p(R/DC) = 0.75, p(R/CC) = 0.5, and p(D) = 0.845; for Annett's model [1985], p (R/DD) = 0.9934, p(R/DC) = 0.9162, p(R/CC) = 0.61, and p(D) = 0.57. Values of N are sample sizes needed for power of 0.80 at the 0.05 level of significance in testing $\phi$.

of 15,675.5 males, 12.7% of them left-handed, and 13,833.9 females, 11.1% of them left-handed.

Table III shows the frequencies of different sibling combinations, along with SS/OS ratios, values of $\phi$, and associated $\chi^2$. The frequencies are not integers because each pair was weighted by 2/N, where N is the number of siblings in the family, to correct for non-independence of pairs [Suarez and Van Eerdewegh, 1984]. The overall $\phi$ of 0.0215 is highly significant ($P < 0.01$), confirming the concordance between handedness and sex. The $\chi^2$ is also significant ($P < 0.05$) for the offspring of parents who are both right handed. These results give broad support to a genetic locus on the sex chromosomes. For other parental pairs the sample sizes were too small to provide adequate statistical power. The only aspect of the overall data at variance with expectation is that the SS/OS ratio was less than unity for left-handed pairs, but this may not be a reliable effect since the sample was small.

The $\phi$ coefficients might have been biased by the slight preponderance of males. Since the males were more likely to be left-handed than the females, male siblings were also more likely to be of opposite handedness than female siblings, and therefore to have contributed disproportionately to the SS frequency among siblings of opposite handedness. To check this, the values in the rows of the table for the total sample were proportionally adjusted to even the numbers of males and females (i.e., so that the totals of the rows were in proportion 1 : 2 : 1) while keeping the total constant. This raised the value of $\phi$ to 0.0232 and the $\chi^2$ to 7.96 ($P < 0.005$).

That the overall $\phi$ is close to that predicted by the genetic models supports complete rather than partial X-Y linkage, that is, an homologous gene in the sex-specific, rather than in the pseudo-autosomal, region of the sex chromosomes. As with pseudo-autosomal genes, it appears that X-Y linked genes are protected from X-inactivation [Fisher et al., 1990]. Owing to transpositions, some genes are likely to have become X-Y homologous in recent hominid evolution [Lambson et al., 1992]; moreover, X-Y homologous genes imply the absence of recombination, so that the X and Y copies are free to diverge. Since only males could possess the Y-linked sequence, the gene would be subject to sexual selection [Crow, 1993b], which might account for the sexual dimorphism claimed for cerebral asymmetry [McGlone, 1980]. Darwin considered just such a mechanism to be of critical importance for human evolution [Darwin, 1871].

TABLE II. Respondents in Five Surveys of Handedness

| | Males | Females | Sibling pairs (corrected) |
|---|---|---|---|
| 1st Cambridge survey [McManus, 1979] | 1608 | 1134 | 2007.2 |
| 2nd Cambridge survey [McManus, 1979] | 1765 | 1547 | 2176.9 |
| NCES[a] [Madge et al., 1993] | 5521 | 5459 | 7331.3 |
| New Zealand survey | 2359 | 2635 | 2888.8 |
| British Columbia Survey [Coren and Porac, 1980] | 307 | 395 | 351.0 |

[a]NCES, British National Childhood Encephalopathy Study; numbers of sib pairs were corrected by the method of Suarez and van Eerdewegh, 1984.

TABLE III. Accumulated Data on the Concordance of Handedness and Sex Among Sibling Pairs. $\phi$, the Product-Moment Correlation (of Handedness in One Sibling With Handedness in the Other) = $\sqrt{\chi^2/n}$]*

| Parental pairs (Mother × father) | Sex pairings | Offspring: Handedness pairings R × R | R × L | L × L |
|---|---|---|---|---|
| R × R | M × M | 2847.4 | 663.3 | 60.8 |
| | M × F | 4728.8 | 1122.8 | 98.8 |
| | F × F | 2227.7 | 418.0 | 30.2 |
| | SS/OS | 1.073 | 0.963 | 0.921 |
| | | $\phi = 0.0203$, $\chi^2(1) = 5.018$, $P < 0.05$ | | |
| R × L | M × M | 159.3 | 74.1 | 17.4 |
| | M × F | 313.5 | 165.9 | 31.0 |
| | F × F | 170.5 | 74.0 | 12.4 |
| | SS/OS | 1.052 | 0.893 | 0.961 |
| | | $\phi = 0.0361$, $\chi^2(1) = 1.326$, NS | | |
| L × R | M × M | 191.7 | 108.2 | 19.5 |
| | M × F | 312.0 | 172.7 | 34.9 |
| | F × F | 148.0 | 80.2 | 15.6 |
| | SS/OS | 1.089 | 1.091 | 1.006 |
| | | $\phi = -0.0023$, $\chi^2(1) = 0.006$, NS | | |
| L × L | M × M | 13.5 | 6.7 | 7.3 |
| | M × F | 28.4 | 17.3 | 5.0 |
| | F × F | 15.6 | 8.5 | 3.2 |
| | SS/OS | 1.025 | 0.879 | 2.100 |
| | | $\phi = 0.0691$, $\chi^2(1) = 0.504$, NS | | |
| Totals | M × M | 3257.9 | 865.3 | 106.0 |
| | M × F | 5511.7 | 1530.7 | 175.7 |
| | F × F | 2641.8 | 602.7 | 63.4 |
| | SS/OS | 1.068 | 0.950 | 0.948 |
| | | $\phi = 0.0230$, $\chi^2(1) = 7.99$, $P < 0.005$ | | |

* The totals exceed those in the columns above because they include data from Coren's survey [1980] which did not record parental handedness. Sibling pair totals are weighted for multiple sibships according to Suarez and van Eerdewegh [1984].

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## REFERENCES

Annett M (1985): "Left, Right, Hand and Brain." London: Lawrence Erlbaum.

Coren S, Porac C (1980): Family patterns in four dimensions of lateral preference. Behav Genet 10:338–348.

Crow TJ (1990a): Strategies for biological research: Psychosis as an anomaly of the cerebral dominance gene. In Hafner H, Gattaz WF (eds): "Search for the Causes of Schizophrenia." Berlin: Springer-Verlag, pp 383–396.

Crow TJ (1990b): Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schiz Bull 16:433–443.

Crow TJ (1993a): Origins of psychosis and the evolution of human language and communication. In Langer S, Mendlewicz J, Racagni J (eds): "New Generation of Antipsychotic Drugs: Novel Mechanisms of Action." Basel: Karger, pp 39–61.

Crow TJ (1993b): Sexual selection, Machiavellian intelligence and the origins of psychosis. Lancet 342:594–598.

Darwin C (1871): "The Descent of Man, and Selection in Relation to Sex" (facsimile of original published by J Murray in 1981, London). New Jersey: Princeton University Press, pp 390–402.

Fisher EMC, Beer-Romero P, Brown LG, et al. (1990): Homologous ribosomal protein genes on the human X and Y chromosomes: escape from X inactivation and possible implications for Turner syndrome. Cell 63:1205–1218.

Green MF, Satz P, Smith C, Nelson LD (1989): Is there atypical handedness in schizophrenia? J Abnormal Psychology 98:57–61.

Lambson B, Affara NA, Mitchell M, Ferguson-Smith MA (1992): Evolution of DNA sequence homologies between the sex chromosomes in primate species. Genomics 14:1032–1040.

Madge N, Diamond J, Miller D, et al. (1993): The National Childhood Encephalopathy Study: A ten year follow-up. Dev Medicine Child Neurol (Suppl. 68).

McGlone J (1980): Sex differences in human brain asymmetry: A critical survey. Behav Brain Sci 3:215–263.

McManus IC (1979): "Determinants of Laterality in Man." Ph D thesis, Unpublished.

McManus IC (1985): Handedness, language dominance and aphasia: A genetic model. Psychol Med, Monograph Supplement, 8:1–40.

Suarez BK, Van Eerdewegh PA (1984): Comparison of three affected sib-pair scoring methods to detect HLA-linked disease susceptibility genes. Am J Hum Genet 18:135–146.