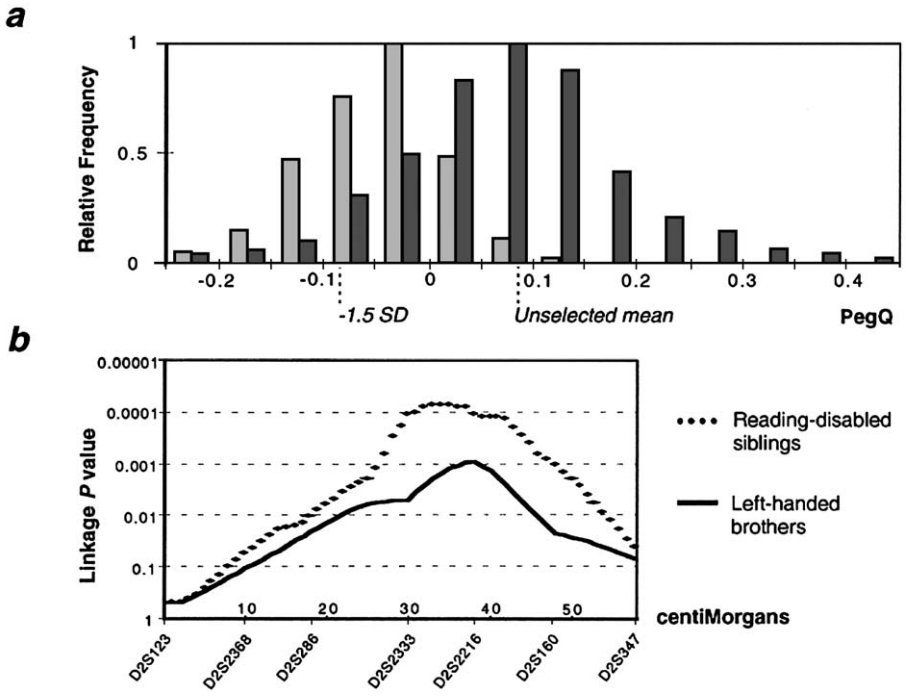

Figure 1 *a*, PegQ distribution in 222 siblings with RD who appeared normal for this measure and were previously analyzed genomewide for linkage (*black*) and in 338 left-writing-handed brothers from whom the current study sample was drawn (*gray*). Positive scores indicate superior relative right hand 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.

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

To the Editor:

We previously reported in the *Journal* the first genome-wide 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 sibship 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.

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