# Parent-of-origin effects on handedness and schizophrenia susceptibility on chromosome 2p12–q11

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**Schizophrenia and non-right-handedness are moderately associated, and both traits are often accompanied by abnormalities of asymmetrical brain morphology or function. We have found linkage previously of chromosome 2p12–q11 to a quantitative measure of handedness, and we have also found linkage of schizophrenia/schizoaffective disorder to this same chromosomal region in a separate study. Now, we have found that in one of our samples (191 reading-disabled sibling pairs), the relative hand skill of siblings was correlated more strongly with paternal than maternal relative hand skill. This led us to re-analyse 2p12–q11 under parent-of-origin linkage models. We found linkage of relative hand skill in the RD siblings to 2p12–q11 with $P = 0.0000037$ for paternal identity-by-descent sharing, whereas the maternally inherited locus was not linked to the trait ($P > 0.2$). Similarly, in affected-sib-pair analysis of our schizophrenia dataset (241 sibling pairs), we found linkage to schizophrenia for paternal sharing with $LOD = 4.72$, $P = 0.0000016$, within 3 cM of the peak linkage to relative hand skill. Maternal linkage across the region was weak or non-significant. These similar paternal-specific linkages suggest that the causative genetic effects on 2p12–q11 are related. The linkages may be due to a single maternally imprinted influence on lateralized brain development that contains common functional polymorphisms.**

## INTRODUCTION

Post-mortem and magnetic resonance imaging (MRI) studies have shown associations between schizophrenia (OMIM 181500) and abnormal asymmetrical morphologies of diverse brain structures (1). Data are generally consistent with a reduction or reversal of left > right volume asymmetry in schizophrenic individuals compared with normal controls, which can affect structures including the medial temporal lobe, superior temporal gyrus, planum temporale, and the overall brain anterior–posterior torque (1,2). Thus, Crow *et al.* (3) proposed that schizophrenia may be a disorder of genetic mechanisms that control the development of cerebral asymmetry.

Non-right-handedness is also associated with reductions or reversals of normal cerebral anatomical and functional asymmetries, particularly for structures related to language processing (4–6). Data from twins suggest that this association

is in part genetically mediated (7,8). Unlike humans, the great apes show no clear population biases towards right-handedness (9). Together, these observations suggest that handedness (OMIM 139900) and complex human cognition are evolutionarily and developmentally related, although the nature and extent of these relationships remain uncertain. Any disruption of asymmetrical brain development could potentially influence both complex cognition and handedness, and evidence exists for moderate phenotypic associations between non-right-handedness and a range of neuropsychiatric conditions, including schizophrenia (10,11). One study found an odds ratio of 5.2 for mixed handedness in schizophrenics versus normal controls (11).

We have previously used quantitative genetic linkage analysis to demonstrate (12), and then to confirm (13), that a locus on chromosome 2p12–q11 influences relative hand skill, a continuous trait which is correlated strongly with handedness

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as defined by writing hand (12). The 2p12–q11 locus showed the strongest linkage to relative hand skill in our genome-wide screen of 191 reading-disabled sibling pairs ($P = 0.00007$, genome-adjusted $P \approx 0.05$) (12). Although the siblings in that study were recruited for analysis of reading disability (RD), their mean relative hand skill was the same as for normal controls, and the reading-related measures that we employed were not correlated with relative hand skill, nor linked to 2p12–q11 (12). This remains the only genome-wide screen performed so far for a measure related to handedness. We failed to replicate the 2p12–q11 linkage in a separate sample of RD siblings (12), but we then replicated the linkage using the same measure of relative hand skill in an independent sample of 105 pairs of adult left-handed brothers ($P = 0.0009$) (13). The existence of the 2p12–q11 quantitative-trait-locus (QTL) was therefore confirmed (13), although the pattern of results suggests that relative hand skill has a multifactorial etiology.

In a separate study, DeLisi *et al.* (14) performed a genome-wide linkage screen with 382 affected sibling pairs drawn from 294 families with at least two siblings affected with schizophrenia or schizoaffective disorder. An association between schizophrenia and non-right-handedness has been found previously in this sample (11). The second strongest linkage in that genome screen was centred on 2p12, LOD = 2.99, pointwise $P = 0.00021$, although this was only suggestive of linkage when adjusted for multiple testing in a genome-wide context. However, the LOD score was higher and reached genome-wide significance if only those with a narrower phenotype of chronic schizophrenia were considered as affected (unpublished data). In addition, some independent, weaker linkages to schizophrenia have been reported around the centromeric region of chromosome 2 (14), and a recent meta-analysis of 20 genome-wide linkage screens for schizophrenia that included the sample of DeLisi *et al.* (14) found that 2p12–q22 showed the strongest evidence for linkage in the genome (15).

In the present study we observed that in our sample of RD siblings that was used for the genome-wide screen (12), the relative hand skill of siblings was correlated more strongly with paternal than maternal relative hand skill. Since 2p12–q11 had shown the strongest linkage to this trait anywhere in the genome, we reasoned that this locus may partly or wholly explain the paternal correlation within this sample, and we therefore re-analysed 2p12–q11 under parent-of-origin linkage models. This led us in turn to re-analyse 2p12–q11 in relation to schizophrenia using the sample of DeLisi *et al.* (14), including linkage analysis with parent-of-origin methods. In these analyses, identity-by-descent sharing was partitioned into separate paternal and maternal components by use of parental genotype data. We had no parental data available for the sample of left-handed brothers (13), so we were unable to include that dataset in the present study.

## RESULTS

### Correlation analysis

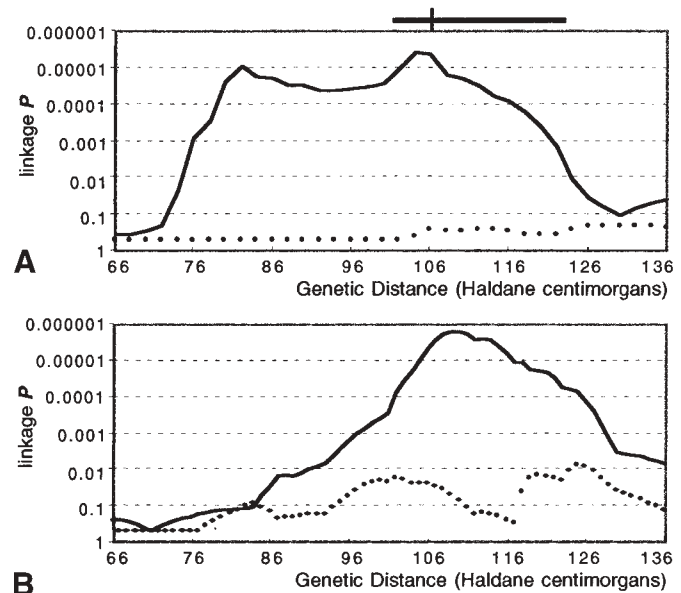The reading-disabled sample comprised 88 independent nuclear families, including 191 sibling pairs. Correlations for



**Figure 1.** (**A**) Paternal linkage of relative hand skill to chromosome 2p12–q11 in 191 reading-disabled sibling pairs. *x*-Axis; chromosome region spanning 2p21–q14 (given as genetic distance from marker D2S2259). *y*-Axis: significance of linkage under regression analysis (see Methods). Solid curve, paternal linkage; dashed curve, maternal linkage. The thick horizontal line (above) represents the maximally linked interval in our analysis of relative hand skill in a separate sample of 105 pairs of adult left-handed brothers (13), for which no parent-of-origin analyses are possible (the vertical stroke is the maximally linked locus in that sample). (**B**) Linkage of schizophrenia to 2p12–q11 in 241 affected sibling pairs. Solid curve, paternal linkage; dashed curve, maternal linkage.

relative hand skill in this sample were: father : child $r = 0.19$, SE $= \pm 0.08$; mother : child $r = 0.07$, SE $\pm 0.08$; sib : sib $r = 0.24$, SE $= \pm 0.09$. Thus the mother : child correlation was not significant at $\alpha = 0.05$, while the paternal correlation was significant and roughly equalled the sibling correlation, suggesting that paternal transmission was primarily responsible for the familial clustering of the trait in this sample.

### Parent-of-origin linkage analysis of relative hand skill

Sib-pair regression analysis yielded a peak paternal linkage $t = -4.67$, $P = 0.0000037$, to a locus within 2p12 corresponding to the position of marker D2S139 (Fig. 1). In contrast to this strong paternal linkage, there was no significant evidence across the 70 cM region that we studied for maternal linkage to relative hand skill (all $t > -0.83$, $P > 0.20$). Consistent with this, maximum likelihood variance components modelling with independent paternal and maternal QTL effects yielded an estimate of the paternal effect roughly five times that of the maternal effect at the peak of linkage (data not shown). This model did not provide a significantly better fit ($P > 0.1$) than a paternal-only effect model, i.e. a model with the maternal effect constrained to zero. Under the paternal-only effect model, the peak linkage LOD score was 2.65, 2 cM proximal to the peak identified with regression analysis. We saw a LOD score as high or higher than this in only three out of 100 000 simulations under the null hypothesis of no linkage, and we can therefore

assign an approximate significance level $P = 0.00003$ under this analysis.

### Linkage analysis of schizophrenia

In affected-sib-pair analysis of schizophrenia and schizoaffective disorder (376 affected sibling pairs with data available for chromosome 2), the LOD score was 3.71 at a location in 2p11, 2 cM from the peaks of linkage to relative hand skill. This was 0.72 LOD units higher than that reported by DeLisi *et al.* (14) (reported LOD = 2.99), and this difference can be attributed to our use of a more recent genetic marker map, together with a different linkage analytical package, and genotype error checking routines (see Methods). The linkage evidence on 2p11 increased to a highly significant LOD = 5.13 when we excluded the individuals affected with schizoaffective disorder and performed affected-sib-pair analysis with the schizophrenia-only phenotype (241 pairs in 196 independent nuclear families). This analysis was not reported by DeLisi *et al.* (14), and it suggested that the 2p12–q11 effect was related to schizophrenia without an affective component to the disorder.

When we performed parent-of-origin affected-sib-pair analysis of this locus for schizophrenia (241 sibling pairs), we found that the peak paternal LOD was 4.72 ($P = 0.0000016$) at a location on 2p11 near to marker D2S417, 3–5 cM from the peaks of paternal linkage to relative hand skill (Fig. 1). In contrast, the evidence for maternal linkage across the region was weak or non-significant, and ambiguous in location (Fig. 1; LOD = 0.6, $P = 0.048$, at the locus corresponding to the maximally linked paternal peak). When the schizoaffective individuals were also included, a similar albeit less striking pattern emerged, with paternal LOD = 3.12, maternal LOD = 1.06, again at different locations (data not shown). Finally, in a separate analysis of the schizophrenia phenotype only, a parametric parent-of-origin linkage modelling approach (16) also identified linkage at the same location, which was consistently strongest under paternal-only-effect models (LOD = 4.14 under one set of model parameters; not shown).

## DISCUSSION

We have found evidence for strong paternal linkages of relative hand skill and schizophrenia to a locus on chromosome 2p12–q11, in separate large samples. Since both handedness and schizophrenia are associated with abnormal asymmetrical brain morphology, and show a degree of association with one another, a shared genetic influence on these traits is *a priori* a possibility. Concordant linkages to different traits in separate samples can usually be no more than suggestive of a common genetic effect. The 2p12–q11 region contains 119 known genes (17), and it is therefore possible that the concordance of linkages that we have identified represents a chance finding, caused by variation in different genes. However, the paternal-specific natures of these linkages, as well as their close positional concordance, provides evidence that the influences on relative hand skill and schizophrenia on 2p12–q11 are related at the genomic level. This is because polymorphic loci that exert parent-of-origin effects are uncommon in the human genome, based on current knowledge (18).

The paternal linkages are suggestive of an imprinted genetic influence on lateralised brain development. Only 49 human imprinted genes are currently known (18). Imprinted genes are differentially expressed from the paternally and maternally inherited chromosomes, and one copy is often inactivated, in part by methylation of gene-regulatory sequences (19). The methylation pattern is erased and subsequently re-established in the germ cells in a manner that is specific to the parental sex (19). Assuming the existence of a single imprinted locus on 2p12–q11, an obvious explanation for paternal linkages is that the maternal gene is inactivated, such that only functional polymorphisms in the paternally inherited gene have an effect on the phenotypes. The weak maternal linkage of schizophrenia to 2p12–q11 that we observed may also be compatible with such a maternal imprinting effect, insofar as additional polymorphisms might exist that affect the degree of maternal inactivation. The neurogenetic disorders Angelman syndrome and Prader–Willi syndrome provide supportive evidence for such a model, as a minority of cases of both syndromes are due to aberrant imprinting and gene silencing (20).

However, there are other possibilities to explain our data, including that the hypothetical gene is normally paternally imprinted, but that most of the relevant polymorphisms influence the degree of inactivation. Since imprinted genes can occur in clusters in the genome (18), it is also possible that polymorphisms within different genes of the same cluster cause variation in relative hand skill and schizophrenia susceptibility. As with all genetic studies of etiologically complex traits, we stress the importance of future replication of our results in independent samples, to confirm that the differences in strength between paternal and maternal linkages that we have observed are not chance findings caused by stochastic variability in identity-by-descent sharing, superimposed on effects that are parent-unspecific. Only the identification of the underlying gene(s) will provide definitive answers about the precise genetic and developmental mechanisms that are responsible for these linkages.

Individuals with uniparental disomy (UPD) for chromosome 2, in which both copies of this chromosome were inherited from a single parent, have been described as phenotypically normal, unless affected by specific 'recessive' conditions in the cases of isodisomy (inheritance of two copies of one template chromosomal region) (20,21). These cases therefore suggest that there are no imprinted genes on chromosome 2 that have major effects on development when both copies are inactivated, and indeed no genes known to be imprinted are located within our region of linkage (18). However, any influence on handedness and schizophrenia susceptibility would necessarily be subtle in its effects on overall development, and there is no reason to assume that the relevant polymorphisms would result in the complete loss of function of any putative imprinted gene on 2p12–q11.

Imprinted genes are often involved in controlling growth, which suggests that they have adapted to maximize their replication against a background of paternal–maternal conflict over resource allocation to offspring (19,22). Our results therefore raise the intriguing possibility that lateralized development of the human brain, and complex human cognitive abilities, have been subject to a parental conflict over investment that has influenced their evolution. This may relate conceivably to the

extremely protracted period of postnatal care that is demanded by human children before they develop cognitive and behavioral independence, compared with other mammals.

Imprinted loci can show markedly different male–female recombination rates (19). However, owing to software constraints for quantitative parent-of-origin linkage analysis, all of our multipoint analyses were performed used the same sex-averaged framework marker map (see Materials and Methods). Kong *et al.* (23), in their study of 1257 meioses using 5136 microsatellite markers genome-wide, published data that showed a female : male recombination rate ratio as high as 11.1 for one interval in 2p11. Nonetheless, this is unlikely to have had a biasing effect on our linkage analyses. The multipoint polymorphism information content (PIC) at the peak of paternal linkage to relative hand skill, in the RD siblings, was greater than 95%, owing to the relatively high number of microsatellite markers for which we have genotype data (see Materials and Methods). Therefore the estimates of paternal and maternal identity-by-descent sharing at this locus should not be significantly biased. Furthermore, to check the validity of the paternal effect on schizophrenia, we repeated the parent-of-origin affected-sib-pair analysis with sex-specific maps [as published by Kong *et al.* (23)], using the same analysis package as for our main analysis (the ASPEX package (see Materials and Methods) accepts different male–female maps as simultaneous input). The difference between paternal and maternal LOD scores remained >4 LOD units under this analysis (data not shown).

The paternal linkage of 2p12–q11 to relative hand skill in our RD sample is in accord with the stronger father–child than mother–child correlation for this trait in this sample. Epidemiological studies of left-handedness have tended to find a stronger mother–child than father–child association (24), which suggests that the 2p12–q11 effect is one of a multifactorial range of influences on handedness. However, no large-scale epidemiological studies have so far analysed a continuous measure of relative hand skill. A multifactorial etiology for relative hand skill is further suggested by our second sample of reading-disabled sibling pairs (see Introduction), which has failed to show linkage of 2p12–q11 to this trait in standard analysis, and now continues to show no significant linkage under parent-of-origin analysis ($P > 0.05$, data not shown). This second sample also shows very weak parent–child and sib–sib correlations, which may be due to increased noise in the measure arising from the lower age of the siblings in this sample (mean age 11 years compared with 14.5 years in the current study RD sample) (12).

There is no consistent evidence for a higher paternal than maternal offspring-relative-risk for schizophrenia (25), and indeed previous analyses of the pattern of inheritance in the present study sample have not shown significant evidence for either predominantly paternal or maternal transmission (25). This epidemiological evidence underscores once more the need for replication of our results in independent samples. However, the 2p12–q11 locus may be one genetic effect, the influence of which is masked in epidemiological studies by a complex overall background for this condition. Therefore we encourage researchers of schizophrenia and handedness to re-analyse any available genetic data from 2p12–q11 under parent-of-origin models.

## MATERIALS AND METHODS

### Family samples

Parent-of-origin analyses of relative hand skill were performed using our sample of 191 sibling pairs from 89 independent nuclear families, which has formed the first sub-sample of our on-going study of the genetics of reading disability (26), and in which a full genome-wide screen was performed previously (12,27). The families were recruited clinically through at least one reading-disabled proband, with a requirement for evidence of reading problems in at least one sibling of the proband (26,27). Relative hand skill was assessed for all probands and all available siblings and parents in each nuclear family, using Annett's peg moving task (12,28). The task involves measuring the time taken, with each hand, to move a row of pegs from one location on a board to another. Relative hand skill was then derived as $(L - R)/[(L + R)/2)]$, i.e. the difference between mean left and right hand times (over five trials per hand), adjusted for overall hand skill. This continuous measure of relative hand skill, termed PegQ by us in previous publications (12,13), has a roughly normal population distribution with a positive mean that reflects the preponderance of right-handedness in unselected populations (12,13). The RD siblings score as an unselected population for this measure (12). We have found that this measure of relative hand skill is not correlated with overall motor coordination ($r = 0.02$, $P = 0.39$), the latter measure having been calculated as residuals from a linear regression of $(L + R)/2$ on age within the RD sibling sample (29).

Analysis of schizophrenia/schizoaffective disorder was performed using the sample and genetic marker data described by DeLisi *et al.* (14), which included 196 independent nuclear families with at least two siblings affected by schizophrenia according to DSM-III-R criteria, for a total of 241 affected sibling pairs (or 376 affected pairs with either schizophrenia or schizoaffective disorder). Diagnoses were made on the basis of structured interviews, review of medical records, and structured information obtained from at least one reliable family member (14). Although questionnaire-based handedness data are available for part of this sample (69 sib pairs) (11), the frequency distribution of this measure rendered it unsuitable for use in linkage analysis (bimodal, with severe floor and ceiling effects).

### Correlation analysis

Correlations for relative hand skill between relative pairs in the reading-disabled sample were calculated using the program FCOR from the software package SAGE4.4 (30), giving equal weight to independent families.

### Parent-of-origin linkage analysis of relative hand skill

Multipoint parent-specific identity-by-descent (IBD) sharing probabilities for sibling pairs, at 2 cM intervals across a 70 cM region of chromosome 2, were derived using the program Merlin (31). The probabilities were converted to parent-specific IBD sharing proportions. Linkage analysis was performed in two ways. First, we linearly regressed squared sib-pair trait differences simultaneously but separately on paternal and maternal IBD sharing for all sib pairs, and obtained

conservative pointwise significance levels via the one-tailed *t*-test using degrees of freedom equal to the number of unique pairings in the sample (131 pairs). This analysis was therefore analogous to classical Haseman–Elston regression (32,33). Second, we used a modified version of the program Multic (34) to perform maximum likelihood variance components analysis in which paternal and maternal effects of the locus were free to vary independently in the full model (34), again by using the multipoint IBD output from Merlin. We used only sibling phenotype data in this analysis. Since the maternal effect of the locus was found to be low (see Results), we constrained this effect to be zero in the full linkage model, in order to obtain optimal positional resolution for the paternal QTL. The empirical pointwise significance of linkage under this model was assessed using a simulation method that we have described previously (12,13,29).

The same genetic marker map was used throughout our analyses of all samples in this study. As a framework we used the sex-averaged map described by Kong *et al.* (23), with additional markers inserted according to their physical locations on the November 2002 genomic sequence build (17), which was verified by bioinformatic analysis across the region of interest. This is in contrast with the previous study of the schizophrenic siblings by DeLisi *et al.* (14), who used a map derived from the sample data themselves (14).

### Linkage analysis of schizophrenia

We extracted the nuclear sibling-pair families from the full family dataset, and used the sib-phase program of the ASPEX package (35) to calculate multipoint affected-sib-pair linkage LOD scores allowing for dominance variance, and across the same 70 cM interval as for our relative hand skill analyses. We then used the sex-split option in ASPEX to obtain LOD scores that were specific to paternal or maternal sharing. [In contrast, DeLisi *et al.* (14) had used the program MAPMAKER/SIBS (14) for their multipoint analyses.]

### Genotyping

The analyses of relative hand skill were performed using highly polymorphic microsatellite marker data from nine markers additional to the 26 described previously within this region (12,36), which now yielded an average intermarker interval of 2.1 cM across the region. Polymorphic microsatellite markers were genotyped according to standard protocols (27). The analysis of schizophrenia was performed with existing genotype data (14), including 20 microsatellite markers within the 70 cM region (average intermarker interval 3.7 cM). Prior to performing linkage analyses, we applied a genotype error-detection method (31) to both datasets, that identifies unlikely patterns of recombination and eliminates suspect genotypes [this was not used by DeLisi *et al.* (14)].

## ACKNOWLEDGEMENTS

## NOTE ADDED IN PROOF

A genome-wide linkage screen for left-handedness was published in October 2003, which did not produce evidence for linkage to 2p12–q11. However, the sample size was small (25 nuclear families) and the phenotype was dichotomous (38).

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