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ORIGINAL ARTICLE

Genome-wide association study of handedness excludes simple genetic models

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Handedness is a human behavioural phenotype that appears to be congenital, and is often assumed to be inherited, but for which the developmental origin and underlying causation(s) have been elusive. Models of the genetic basis of variation in handedness have been proposed that fit different features of the observed resemblance between relatives, but none has been decisively tested or a corresponding causative locus identified. In this study, we applied data from well-characterised individuals studied at the London Twin Research Unit. Analysis of genome-wide SNP data from 3940 twins failed to identify any locus associated with handedness at a genome-wide level of significance. The most straightforward interpretation of our analyses is that they exclude the simplest formulations of the 'right-shift' model of Annett and the 'dextral/chance' model of McManus, although more complex modifications of those models are still compatible with our observations. For polygenic effects, our study is inadequately powered to reliably detect alleles with effect sizes corresponding to an odds ratio of 1.2, but should have good power to detect effects at an odds ratio of 2 or more.
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INTRODUCTION

Although exhibiting bilateral symmetry externally, human anatomy is fundamentally asymmetrical, as displayed most strikingly by the viscera. The detailed relationships between neural function and brain structure are also clearly asymmetrical, reflected in laterality of modular brain functions, and (in most individuals) in strong laterality preferences for fine hand movements and other complex motor functions (Rentería, 2012; Bishop, 2013). Handedness may result in part from learning, but most evidence has supported an innate and possibly even prenatal origin (Hepper *et al.*, 1998); co-occurrence of handedness in families suggested that handedness may be genetically determined, and some of the earliest models involve relatively simple mechanisms.

The 'right-shift' model of Annett (Annett, 2002) postulates codominant alleles (rs+ and rs−) at a single handedness locus. All three genotypes (rs+/rs+, rs+/rs− and rs−/rs−) include both right- and left-handed individuals, but each additional dose of the rs+ allele shifts the probability towards right-handedness. By contrast, in the 'dextral/chance' model of McManus (McManus, 1985), handedness is the result of the influence of two codominant alleles (D = dextral and C = chance); homozygotes for CC have a 50:50 probability of being right- or left-handed, heterozygotes CD have a 25% chance of being left-handed, whereas DD individuals are all right-handed.

In principle, a simple genetic influence of this kind should be evident in comparisons between monozygotic and dizygotic twins, with heritability demonstrable as significantly greater concordance between monozygotic than dizygotic co-twins, as clearly shown in the meta-analysis of Sicotte *et al.* (1999). Twinning itself has been suggested as a confounding factor in various studies, especially if there is a bias towards opposite handedness in co-twins ('mirror' twins'), although there is no robust evidence for the phenomenon of mirror-twinning (McManus, 1980). Some workers have laid greater emphasis on the evidence from segregation in pedigrees for heritable factors, where there is undoubtedly an increased likelihood for the offspring of left-handed parents to be left-handed themselves (McManus and Bryden, 1992). This divergence between twin and family evidence may arise in part from many studies having relatively small sample sizes (Medland *et al.*, 2006; 2009); by contrast, a 2009 study examining over 50 000 twins and their non-twin siblings showed no evidence for twinning- or sex-specific effects on handedness and concluded that about 25% of the phenotypic variance was attributable to additive genetic factors, with nearly all of the remainder attributable to non-shared environmental factors (Medland *et al.*, 2009). This value of ∼25% for the additive genetic component is also compatible with the conclusions of a study of more than 30 000 twins in the Finnish Twin Cohort (Vuoksimaa *et al.* 2009). Although a level of 25% for the contribution of additive genetic factors to the overall variation does not appear to be consistent with the original formulations of the Annett or McManus models, without genotyping data it is not possible to exclude the existence of individual loci of strong effect on the handedness phenotype. To date, linkage and association studies have been confined to relatively few individuals (Francks *et al.*, 2002; 2007; Scerri *et al.*, 2011), so that there has been relatively low power to definitively exclude the existence of major loci influencing human handedness. In particular, alleles at *LRRTM1* and *PCSK6* implicated in linkage to or association with handedness in learning-disabled

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subjects have not been replicated in cohorts of non-disabled individuals (Francks *et al.*, 2002; 2007; Scerri *et al.*, 2011).

Other approaches to explaining the observed patterns of familial clustering for variation in cerebral asymmetry have been suggested, including the emergence of variation in handedness from gene-culture interactions (Laland, 2008) or from the combination of a fixed right-shift factor with variation due to (transmissible) epigenetic modification (Crow, 2009).

The availability of platforms for genome-wide typing of common genetic polymorphisms allows a different approach to determining the possible genetic basis for the determination of human handedness. Any allele underlying the models of McManus or of Annett, or any other simple genetic model in which handedness is determined by the inheritance of a pair of alleles, would need to have both a high frequency in the population (to account for the approximately 10% incidence of left-handedness) and to exert a strong individual effect on handedness phenotype. If so, such an allele should be effectively tagged by modern SNP-typing platforms, and even relatively small sample sizes should allow detection of highly significant association with handedness. In effect, a study investigating even as few as several hundred subjects with genome-wide SNP genotypes should leave such an allele nowhere to hide in the genome, and even determinants considerably weaker than those of Annett or McManus (but still strong by the general standards of polygenic traits) should be convincingly demonstrable; conversely, failure to demonstrate such an association should allow the exclusion of simple genetic models involving strong effects of single alleles.

In this study, we aimed to search the genome for alleles strongly associated with handedness, so that we could either provide initial evidence for a locus of strong effect or, after an exhaustive search, exclude simple genetic models from future consideration. In this work, we examined association of handedness under simple genetic models in a total of nearly 4000 individuals.

MATERIALS AND METHODS

Twin genotypes and phenotypes

Our study analysed SNP genotype and handedness phenotype data that had already been collected at the Department of Twin Research, King's College London as part of their comprehensive analysis of twin pairs. Handedness phenotype was determined at the Twin Research Unit by collating responses to a questionnaire that included a question about handedness. At different times, this question was either 'are you right handed or left handed (if you are not sure, which hand do you write with?)' or 'which hand do you write with?'. The handedness phenotype we use can therefore be largely viewed as equivalent to writing hand preference.

SNP genotypes for twins were determined with a combination of Illumina arrays (HumanHap300(Richards *et al.*, 2008; Soranzo *et al.*, 2009), HumanHap610Q, 1 M-Duo and 1.2MDuo 1 M). Normalised intensity data (Kermani, 2006) were pooled for each of the three arrays separately (with 1 M-Duo and 1.2MDuo 1 M pooled together). For each data set the Illuminus calling algorithm (Teo *et al.*, 2007) was used to assign genotypes in the pooled data. No calls were assigned if an individual's most likely genotype was called with less than a posterior probability threshold of 0.95. Validation of pooling was achieved via a visual inspection of 100 random, shared SNPs for overt batch effects. Finally, intensity cluster plots of significant SNPs were visually inspected for over-dispersion-biased no calling and/or erroneous genotype assignment. SNPs exhibiting any of these characteristics were discarded.

Similar quality control exclusion criteria were applied to each of the three data sets separately. The exclusion criteria for samples were (i) sample call rate $<98\%$, (ii) heterozygosity across all SNPs $\geqslant 2$ s.d. from the sample mean, (iii) evidence of non-European ancestry as assessed by PCA comparison with HapMap3 populations, (iv) observed pairwise IBD probabilities suggestive of sample identity errors and (v) misclassified monozygotic and dizygotic twins were corrected based on IBD probabilities. The exclusion criteria for SNPs were (i) Hardy–Weinberg P-value $<10^{-6}$, assessed in a set of unrelated samples, (ii) MAF $<1\%$, assessed in a set of unrelated samples, (iii) SNP call rate $<97\%$ (SNPs with MAF$\geqslant 5\%$) or $<99\%$ (for $1\% \leqslant$ MAF $< 5\%$). Alleles of all three data sets were aligned to HapMap2 or HapMap3 forward strand alleles.

Before merging, pairwise comparison was performed among the three data sets and further excluded SNPs and samples to avoid spurious genotyping effects, identified as follows: (i) concordance for duplicate samples $<1\%$; (ii) concordance for duplicate SNPs $<1\%$; (iii) visual inspection of QQ plots for logistic regression applied to all pairwise data set comparisons; (iv) Hardy–Weinberg P-value $<10^{-6}$, assessed in a set of unrelated samples; (v) observed pairwise IBD probabilities suggestive of sample identity errors. The three data sets were then merged, keeping individuals typed at the largest number of SNPs when an individual was typed with two different arrays. The total merged data set consisted of 5654 individuals (2040 from the HumanHap300, 3461 from the HumanHap610Q and 153 from the HumanHap1M and 1.2 M arrays) and up to 874 733 SNPs depending on the data set (HumanHap300: 303 940, HumanHap610Q: 553 487, HumanHap1M and 1.2 M: 874 733). Imputation was performed using IMPUTE (v2) (Howie *et al.*, 2009) using two reference panels, P0 (HapMap2, rel 22, combined CEU + YRI + ASN panels) and P1 (610k+, including the combined HumanHap610k and 1 M reduced to 610k SNP content).

GWAS methods

We performed genome-wide association analysis with SNPTEST v2 (Marchini *et al.*, 2007; Wellcome Trust Case Control Consortium, 2007) using an additive frequentist model and the option '-method threshold' to assign individual genotypes. This analysis adopted $\alpha = 5 \times 10^{-8}$ as a conventional threshold for significance in a genome-wide study (Dudbridge and Gusnanto, 2008).

Power simulations

To determine the power of our study to detect loci responsible for the determination of handedness under different genetic models, we undertook Monte Carlo simulations of a cohort of 2355 individuals (simulating the numbers used in 'set 1') drawn from a population in Hardy–Weinberg equilibrium. The simulation assumed 10% left-handed individuals, and genotypes for the 'causative' locus were assigned to each simulated individual with probabilities derived from the model being tested. However, the SNP platform used will be very unlikely to include by chance the causative locus, and in practice the simulation needs to model power based on realistic assumptions about how well the best-associated SNP on the platform will tag the (unknown) causative locus. Approximate distributions drawn from the analysis of Spencer *et al.* (2009) were therefore used to derive individual genotypes for the SNP typed on the platform, conditional on both the simulated genotype at the causative locus and the expected distribution of LD between the typed SNPs and an unknown variant, which were then used as the basis of an association test. Simulations of 2355 individuals reaching significance at a P-value below 5×10^{-8} were recorded, and the simulation was run 10 million times for each set of conditions. The estimates of power derived from these simulations will be conservative relative to the real conditions used in our study, because they only simulate the power of set 1 and disregard set 2 (see Results section on GWAS analysis).

The models applied were as follows: 'McManus' is a simple additive model in which a single codominant 'chance' (C) allele results in a 50% probability of being left-handed when homozygous (CC) and a 25% probability when heterozygous (CD), and homozygotes (DD) for the dextral (D) allele are always right-handed (McManus, 1985); 'McManus*' is a 'leaky' variant of the McManus model in which 20% of left-handers are DD; 'McManusx10' is a further variant in which there is not a single chance allele, but 10 equally frequent alleles C_1, C_2, $\ldots C_{10}$, at a single locus, each of which increases the probability of being left-handed under an additive (codominant) model; 'Annett' is the standard 'right-shift' model (Annett, 2002), in which a single codominant (rs+) allele shifts the probability in favour of right-handedness by a factor of about 7.3; and 'OR1.2' and 'OR2' are simple multiplicative models in which the probability of being left-handed is multiplied by the odds

ratio (1.2 or 2.0, respectively) for each dose of a codominant allele (at a population frequency of 0.2). In all cases, inferred population allele frequencies were adjusted, assuming Hardy–Weinberg equilibrium, to allow the different models to conform to a population frequency of left-handers of 10%.

RESULTS

Twin data and concordance

Our analysis used the well-characterised twin pairs from the London Twin Research Unit (Moayyeri *et al.*, 2012). These volunteers are predominantly female; we included male twins in our analysis, but used only same-sex dizygotic twin pairs. Analysis of concordance for handedness (defined by the writing hand) in 1761 dizygotic and 862 monozygotic twin pairs failed to reveal a significant enhancement of concordance in monozygotic twins (Table 1).

Taken at face value, the absence of significantly increased concordance in monozygotic twins excludes simple, highly penetrant genetic factors in handedness, consistent with the observation in well-powered twin studies that additive genetic factors account for about 25% of the observed variance (Medland *et al.*, 2009; Vuoksimaa *et al.*, 2009). Given our sample size, genetic associations between handedness and common SNPs may still be demonstrable and might be detected by GWAS studies of unrelated individuals drawn from the set of twin volunteers. We therefore undertook a GWAS study on 3940 twins who had undergone whole-genome SNP typing on Illumina platforms.

GWAS analysis

In order to maximise the power of our analysis, but still avoid duplicate representation of the same individuals, we divided the data into two sets. In set 1, the group of 2355 individuals analysed was made up of one member drawn at random from the 763 genotyped monozygotic twins and one member drawn at random from each of the 1592 genotyped dizygotic twin pairs; in set 2, we analysed the 1585 remaining members of the dizygotic twin pairs for whom SNP data were available (that is, those excluded from set 1, with 7 out of 1592 failing SNP quality control). In set 1, 263 (11.2%) were left-handed and in set 2, 173 (10.9%). Although the two sets are not independent, so that they could not be used for robust replication of any positive association, whole-genome screening in both set 1 and set 2 allowed our search for putative loci to make most exhaustive use of the available data.

GWAS results and power simulations

We found no evidence of association significant at a genome-wide level of $P = 5 \times 10^{-8}$; a Manhattan plot from analysis of set 1 is shown as an example in Figure 1. The lowest *P*-value in set 1 (2.89×10^{-7}) was found at rs883565 (chromosome 3), and the lowest value in set 2 was 3.83×10^{-7}, at rs296859 (chromosome 9). There was no significant evidence of association with alleles in a region surrounding *LRRTM1* on chromosome 2 previously implicated in association with relative hand skill. We had genotype data from two of the three SNPs defining the associated haplotype in Francks *et al.* (2007) (rs1446109 and rs723524), neither of which showed evidence of association ($P > 0.4$); to screen more inclusively for any indication of association in this region, we analysed all SNPs in an interval of about 300 kb between rs12470088 and rs12615084 to include the wider region studied by Francks *et al.* (2007). The lowest *P*-values recorded in that region were 0.0154 (from 390 *P*-values in set 1) and 0.00755 (from 382 *P*-values in set 2); given the large number of different SNPs analysed in the interval, these lowest *P*-values are at about the level one would expect purely from chance and do not constitute even suggestive evidence for association. Similarly, there was no evidence for association with rs11855415 ($P = 0.12$ in set 1, $P = 0.50$ in set 2), which had been implicated in a study of relative hand preference in reading-disabled individuals (Scerri *et al.*, 2011).

Comparison of data from set 1 and set 2 found no evidence for consistently reduced *P*-values even at lower levels of significance (Figure 2), and quantile-quantile plots of *P*-values against the expectation drawn from a uniform distribution suggested no systematic excess of low *P*-values in the data (Figure 3). Taken at face value, this outcome appears to exclude simple genetic models in which handedness is determined by common alleles at a single locus, but we undertook power simulations to investigate the likelihood that even an analysis involving nearly 4000 subjects might by chance fail to demonstrate such a locus. These simulations incorporated the standard version of published models (McManus, 1985; Annett, 2002) as well as multi-allelic modifications of them and incorporated estimates of the ability of the SNP genotyping platform to tag an unknown SNP (Spencer *et al.*, 2009)(see MATERIALS AND METHODS for details). These simulations (Table 2) demonstrated that our study was adequately powered to find loci involved in the models of McManus (McManus, 1985) and Annett (Annett, 2002) with high probability. A modified, 'leaky' version of the McManus model ('McManus*' in Table 2) in which 20% of left-handers had the DD genotype was also

Table 1 Concordance of handedness between same-sex monozygotic (MZ) and dizygotic (DZ) twin pairs, showing same-sex female (FF) and male (MM) twin pairs separately and then combined

Pair type	*Concordant RR*	*Concordant LL*	*Concordant AA*	*Concordant total*	*Discordant*	*Total*
DZ FF	1257	39	3	1299	314	1613
DZ MM	105	2	0	107	41	148
MZ FF	656	10	1	667	147	814
MZ MM	38	0	0	38	10	48
DZ total	1362	41	3	1406	355	1761
MZ total	694	10	1	705	157	862

Abbreviations: A, ambidextrous; L, left-handed; R, right-handed.

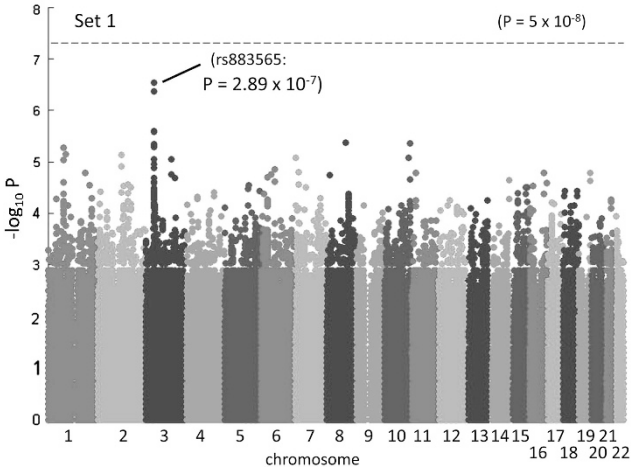

Figure 1 GWAS results for handedness. Manhattan plot of $-\log_{10}$ *P*-values across the genome for association of handedness with 2 535 688 SNPs in Set 1 twins. No points reach a genome-wide significance level of $P < 5 \times 10^{-8}$ (dotted line).

detected with almost full power in the simulations; by contrast, a multi-allelic 'dilution' of the McManus model with 10 different causative alleles at the locus responsible ('McManus x 10' in Table 2) was predicted to be detectable in our study with a probability only a little over 50%. Our study had good (over 90%) power to detect any locus with an odds ratio of 2 in a polygenic model, but poor power to detect an OR of 1.2, which is at the high end of the range of odds ratios observed in multifactorial human phenotypes (Wellcome Trust Case Control Consortium, 2007).

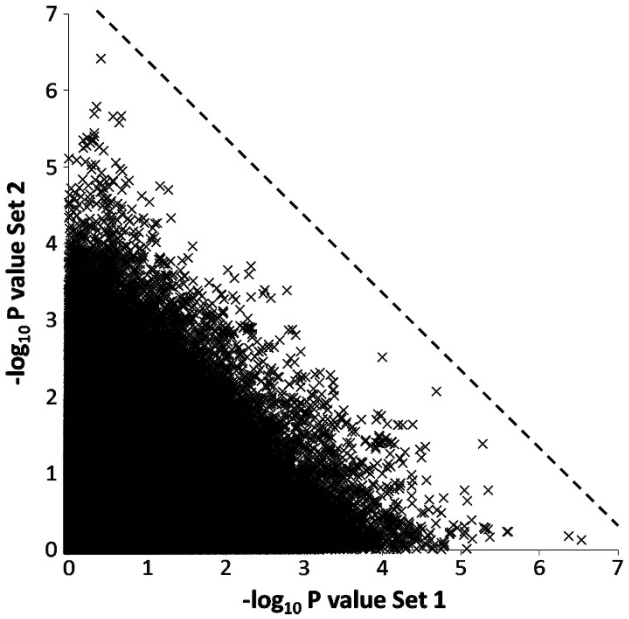

Figure 2 Joint results for association with handedness in Set 1 and Set 2. Joint plot of paired probability values obtained in analysis of Set 1 versus Set 2 for each of 2 499 296 SNPs; the dotted line corresponds to $P_{Set1} \times P_{Set2} = 5 \times 10^{-8}$.

Table 2 Power to detect genetic effects on handedness in Set 1 twins under different genetic models (see MATERIALS AND METHODS for further details)

Model	*McManus*	*McManus**	*McManus × 10*	*Annett*	*OR1.2*	*OR2*
Overall power (%)	99.47	99.07	55.00	99.17	0.022	91.29

DISCUSSION

The simplest interpretation of our data is that they do not support any simple model for the inheritance of variation in handedness and provide evidence to exclude such models with high confidence. Our results are consistent with the results of a larger-scale GWAS study reported in abstract form, but for which full details have not yet been published (Medland *et al.*, 2009). There are nevertheless circumstances under which the specific formulation of our study might lead to failure to detect a true genetic determinant.

First, it is in principle possible that using a cohort consisting entirely of twin subjects constitutes a special case and that our study would have detected a simple genetic influence in a cohort of the same size consisting of singleton births. This consideration, that twinning itself may diminish, distort or overrule genetic factors that determine handedness in non-twins, may also underlie our failure to detect significantly increased concordance of handedness among monozygotic relative to dizygotic twins. However, such twinning-specific effects are not supported by well-powered analyses (Medland *et al.*, 2009), and, in order to destroy the very strong signal of a simple genetic influence that would otherwise be expected in the GWAS, such twin-specific factors would essentially need to almost completely obliterate genetic influences, and only in twins.

Second, it is possible that the SNP genotyping platform used does not, by chance, include any locus that tags the real handedness locus effectively. Even at low levels of LD (for example, $r^2 = 0.2$), our study contains enough subjects to have effectively full power to detect a simple codominant allele. Indeed, for the detection of single-gene factors in handedness, the power of the study is limited primarily not by the number of subjects but by the tagging power of the SNP platform: it is much more likely that a causative variant in the genome similar to those postulated by Annett and by McManus is ineffectively tagged than that a well-tagged variant could escape detection in our study. Nevertheless, the good coverage provided by commercial SNP platforms suggests that situations in which a randomly-chosen locus is tagged at $r^2 < 0.2$ are uncommon, with a frequency of about 2–3% (Spencer *et al.*, 2009).

Finally, power simulations (Table 2) suggest that if there is a single locus determining handedness, it might plausibly escape detection in our study if predisposition to handedness is determined not by a

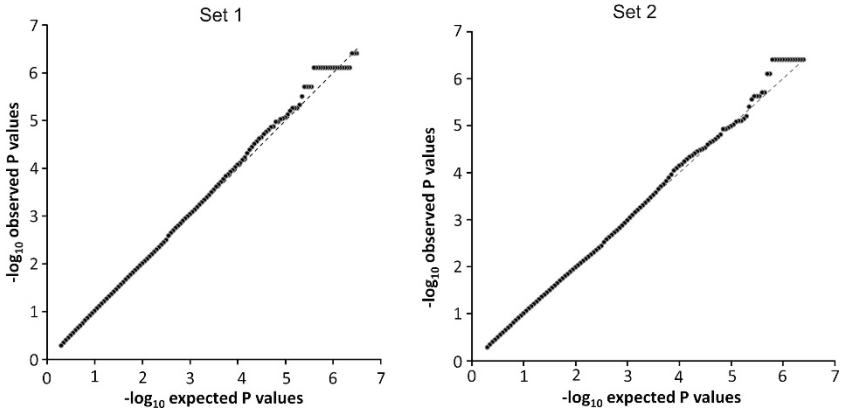

Figure 3 Quantile-quantile plots of GWAS *P*-values against a uniform distribution. Q-Q plots of the distribution of observed $-\log_{10}$ *P*-values for Set 1 and Set 2 against expected values drawn from a uniform distribution, showing no evidence of systematic enrichment for low *P*-values in the observed data.

single determinant at the locus but by any one of a series of independent causative mutations, each of which has the same functional property of altering the probability of the carrier's handedness, but which have arisen independently and are found on different SNP backgrounds, thereby blunting the power of GWAS to detect them. We would predict that if the effect of one locus were due to the combined effect of several independent allelic determinants, this might still be compatible with the population- and pedigree-based patterns observed; our recent theoretical analysis also suggests that it would be difficult to distinguish multilocus models from single-locus models on the basis of their properties in pedigrees and populations (McManus *et al.*, 2013). Nevertheless, the most parsimonious conclusion from our study is that individual genetic factors responsible for handedness variation are likely to be of weak effect, in contrast to the simplest predictions of single-gene models.

DATA ARCHIVING

This article does not report new empirical data or software. The data analysed in this work were collected at the Department of Twin Research, King's College London, and were made available to us after application to the TwinsUK Resource Executive Committee (TREC) – see http://www.twinsuk.ac.uk/data-access/management/.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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