The molecular genetics of hand preference revisited

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Abstract

Hand preference is a prominent behavioural trait linked to human brain asymmetry. A handful of genetic variants showing association with hand preference or relative hand skill have been reported, which implicated the genes *SETDB2, COMT, PCSK6, LRRTM1, SCN11A, AK3, and AR*. Most of these reports were on the basis of limited sample sizes, by current standards for genetic analysis of complex traits. Here we investigated summary statistics from genome-wide association analysis of hand preference in the large, population-based UK Biobank cohort (N=361,194). We also used genome-wide, gene-set enrichment analysis to investigate whether genes involved in visceral asymmetry are particularly relevant to hand preference, following one previous report. We found no evidence implicating any specific candidate variants previously reported, nor more broadly the genes listed above. We also found no evidence that genes involved in visceral laterality play a role in hand preference. It remains possible that some of the previously reported genes or pathways are relevant to hand preference as assessed in other ways, for example by continuous measures, or else are relevant within specific disorder populations. However, some or all of the earlier findings are likely to be false positives, and none of them appear relevant to hand preference as defined categorically in the general population. Within the UK Biobank itself, a significant association implicates the gene *MAP2* in handedness.

Introduction

Hand preference is a conspicuous behavioural trait, with about 10% of people preferring to use their left hand for many tasks, about 1% having no preference, and the large majority preferring to use the right hand [1]. Hand preference is probably initiated during prenatal phases, and further established in early infancy [2-5]. Gene expression analysis has revealed left-right differences in the human central nervous system as early as four weeks post conception [6, 7], which indicates that laterality is an innate and pervasive property of the central nervous system. Across different regions of the world and throughout history, the behavioural variation has persisted, albeit that cultural suppression of left-handedness has sometimes occurred [8-11].

There has been much interest in possible causes of hand preference, as well as its associations with cognitive variation and disorders [12-15]. The existence of a genetic component for hand preference has been investigated in large twin studies, consisting of thousands of individuals. These studies found additive heritabilities of around 25% for left-hand preference [16-19]. In terms of individual genetic loci, monogenic models for hand preference were originally conceived, such as the dextral/chance model [20]. The model proposed that there are two alleles, D (dextral) and C

(chance), with the homozygous DD genotype producing right-handers (directional asymmetry), the homozygous CC genotype producing random asymmetry (50% right-handers and 50% left-handers) due to a hypothesized loss of direction-setting in brain development, and the heterozygote, DC, being intermediate and producing 25% left-handers and 75% right-handers. Another related idea, conceived with respect to continuous measures of left-versus-right hand motor skill, was the 'right-shift' model, which proposed a major gene whose alleles cause either rightward mean asymmetry, or no directional bias [21].

However, genetic linkage analyses in families with elevated numbers of left-handed members have not found convincing evidence for single major genes [22-24]. Genome-wide association scan (GWAS) analysis has also not found any genomic locus with a large enough effect on hand preference to be compatible with monogenic models, unless there would be extensive genetic heterogeneity (i.e. many different Mendelian effects involved in the population)[25]. Meanwhile, as analyses based on twins have indicated 25% heritability, there is clearly ample room for environmental influences, although these remain mostly unknown. Early life variables such as birthweight and twinning can influence handedness, but not to an extent which is remotely predictive at the individual level[26, 27].

Various molecular genetic studies have identified individual genes as potential contributing factors to handedness, with small effects, which would be consistent with a polygenic architecture underlying the heritable component to this trait. We review these genes briefly here:

- A sib-pair analysis (N=89 sibships with reading disability) found suggestive linkage of left versus right relative hand skill, a continuous measure based on the pegboard task [28], to two broad regions on chromosomes 2 and 17 [29]. A follow-up study suggested the signal came from paternal inheritance [30]. Further analysis suggested *LRRTM1* (leucine rich repeat transmembrane neuronal 1) as the most likely gene, as it showed evidence for paternal-specific association with relative hand skill of a particular haplotype, as well as imprinted expression in cell lines [31].
- A CAG-repeat polymorphism in the gene *AR* (androgen receptor), located on chromosome X, has been studied in relation to hand preference, due to a longstanding theory that brain laterality is influenced by sex hormones [32]. One study found association effects which were opposite in males and females for the CAG-repeat [33]. A different study found that right-handedness was associated with shorter CAG repeats in both sexes [34], while another, which only included males, found that mixed-handedness was associated with longer CAG repeats [35].

- In a set of families affected by bipolar disorder, an association was found of a variant in *COMT* (catechol-O-methyltransferase) with relative hand skill, although this did not survive multiple testing correction [36]. *COMT* was studied because it was considered a candidate gene for bipolar disorder [37].
- A study of the genes *SETDB1* (SET domain bifurcated 1) and *SETDB2* (SET domain bifurcated 2) found that the SNP rs4942830 in S*ETDB2* was significantly associated with hand preference as measured as a quantitative trait on the Edinburgh scale [38] (N=950 healthy people), although for the binary trait of left versus right-handedness, the p-value did not survive multiple testing correction [39]. This result was replicated, including the stronger effect for the quantitative trait (right=732, left=75, healthy people)[40]. *SETDB2* was chosen as a candidate for study as it has been shown to regulate structural left-right asymmetry in the zebrafish central nervous system [41].
- A GWAS study of relative hand skill, in a sample of people with reading problems (3-stage design, N=728), found a genome-wide significant association in the gene *PCSK6* (proprotein convertase subtilisin/kexin type 6) [42]. The same research group performed a second GWAS in a cohort of individuals from the general population (N=2666), and found no genome-wide significant associations, and no indication of involvement of *PCSK6* [43]. The GWAS results also yielded evidence that genes influencing visceral asymmetry might be involved in relative hand skill in both the dyslexic group and the general population group. For this analysis, the authors tested sets of genes for an enrichment of association signals in the GWAS data, where the sets were defined based on mutations in mice that influence the organization of the visceral organs on the left-right axis [43].
- In a GWAS study of 263 left vs 2092 right-handers, and 173 left vs 1412 right-handers (this was a study of healthy twins, and the GWAS analysis was divided to achieve non-relatedness of subjects), no genome-wide significant results for self-reported hand preference were found [25]. The most significant associations were near the neighbouring genes *SCN11A/TTC21A/WDR48* (sodium voltage-gated channel alpha subunit 11/ tetratricopeptide repeat domain 21A/ WD repeat domain 48), and *AK3/RCL1* (adenylate kinase 3/ RNA terminal phosphate cyclase like 1) with p<1E-6, i.e. a suggestive level of association which does not survive statistical correction for multiple testing over the whole genome.
- A GWAS of 4268 individuals from the general population, using a questionnaire-based definition of handedness, found no association p-values below 5E-06 in the genome [44]. Possibly other negative results remained unpublished.

110 It has become increasingly clear during the last decade that psychiatric, cognitive and behavioural
111 traits are usually influenced by many genetic factors with very small effects of each individual locus,
112 so that tens of thousands of subjects are needed to detect effects reliably [45]. None of the studies
113 listed above approached that level of sample size or statistical power. Low power reduces the
114 likelihood that a statistically significant result reflects a true effect [46]. Most of the studies
115 summarized above made secondary use of datasets which were collected for different purposes, so
116 that left-handedness was present at only roughly 10% within the datasets. This meant that statistical
117 power was even less than might have been achieved in such sample sizes, for example through
118 selection schemes balanced for handedness. Given the statistical issues affecting the earlier studies,
119 it seems likely, from a contemporary perspective on statistical genetics, that most or all of the
120 findings were false positives.

121 Some of the genetic associations summarized above were identified in groups with specific disorders,
122 including children with reading disability [29, 42], and families with bipolar disorder [36]. Therefore,
123 even if the genetic associations were real, they may not extrapolate to the general population.
124 Finally, a variety of different measures related to handedness were used in these studies, including
125 binary traits based on simple questions such as 'which hand do you write with', to quantitative
126 indices based on the peg board test.

127 An opportunity arose recently to perform a high-powered GWAS of hand preference in a very large,
128 adult population sample from the UK, known as the UK Biobank dataset [47]. A recent study
129 performed separate GWAS for hundreds of different biological variables within this dataset, of which
130 hand preference was just one variable, being available for more than 300,000 subjects (measured by
131 questionnaire and analysed as a set of binary traits, see below). The genome-wide statistical
132 association results from all of the different GWAS were placed on the internet
133 (http://www.nealelab.is/uk-biobank/). Most of the GWAS, including that for hand preference, were
134 not further queried, interpreted or discussed. Two individual loci were significantly associated with
135 hand preference after adjustment for multiple testing over the genome. One locus was within a very
136 large region of linkage disequilibrium which arises from an inversion event on chromosome 17 and
137 spans many genes, while the other was close to the gene *MAP2* (Microtubule Associated Protein 2).
138 However, there may be other loci which are truly associated with hand preference in the UK Biobank
139 GWAS results, but which do not reach the threshold of significance to survive correction for multiple
140 testing over the whole genome (i.e. roughly $P=5x10^{-8}$). SNP-based heritability analysis, based on
141 variation over all of the autosomes (i.e. all chromosomes minus the sex chromosomes) arrived at
142 explained variance (SNP-heritability) for left-handedness of only 1.8% in the UK Biobank (p=6.4e-03),

143 which is markedly lower than previous indications from twin studies (see above), while ambidexterity
144 had an estimated SNP-heritability of 6.8% (p=8.7e-04)[48].

145 Here, we have used the genome-wide GWAS results for hand preference in the UK Biobank to
146 investigate whether any of the previously reported loci, summarized above, show evidence for
147 association with binary trait handedness in the general adult population, as assessed in this large
148 dataset and well powered analysis (http://www.nealelab.is/uk-biobank/). We also applied different
149 methods of gene-set enrichment analysis to the GWAS results, in order to test the relevance of gene-
150 sets that are involved in laterality of the visceral organs.

151 Methods

152 Data

153 We used the data collected in the UK Biobank [47] and analysed by the Neale lab, which were
154 available from www.nealelab.is/uk-biobank/ [49]. Signed informed consent was obtained from all
155 participants, and the UK Biobank has ethical approval from the UK Biobank Research Ethics
156 Committee under number 16/NW/0274. Data for handedness were collected by a questionnaire with
157 the question "Are you right or left handed?", and as possible answers "Left-handed", "Right-
158 handed", "Use both right and left hands equally" and "Prefer not to say"
159 (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1707). The traits investigated in the first release
160 from the Neale lab (September 2017) were left-handed vs 'other' (32,442 left-handed vs 304,688 not
161 left-handed), and ambidextrous vs 'other' (5,517 ambidextrous vs 331,613 not ambidextrous).
162 Heritability estimates as reported above were based on this release. Samples were genetically
163 independent and of white British ancestry [48]. GWAS results were also available from a second
164 release (August 2018, http://www.nealelab.is/uk-biobank/) on 361,194 subjects. This second release
165 included more individuals, updated genotype data, and the addition of the X-chromosome, as well as
166 additional covariates for the association analysis, among which were age and age^2. The analysed
167 traits now also included 'right-handed vs other' (40,671 right-handers vs 320,242 non-right-handers,
168 i.e. ambidextrous individuals were now combined with the left-handers). This is the trait (1707.1)
169 that we predominantly used in the present study for our analyses (below), but we also include look-
170 ups of previously reported candidate SNPs in relation to the 'left-handed versus other' (34,585 cases)
171 and 'ambidextrous versus other' (6,086 cases) results. The GWAS for ambidextrality was necessarily
172 based on a smaller sample size in the 'case' group than the other trait definitions, and accordingly
173 the power would have been lower.

174 The GWAS data summary file provided by the Neale lab included a column
175 "low_confidence_variant". We filtered out the SNPs marked 'true' in this column before further
176 analysis. These were often SNPs with very low minor allele frequency (MAF).

177 Previously implicated SNPs and genes

178 We checked the GWAS catalog (http://www.ebi.ac.uk/gwas/search, 3 July 2018) for the terms
179 'handedness' and 'hand' to find SNPs and genes previously implicated in traits related to hand
180 preference. In addition we checked the literature through Pubmed (July 2018) for (('hand preference'
181 OR 'hand skill' OR 'handedness') AND genetic) to identify SNPs or genes found in non-GWAS studies
182 (such as candidate gene studies). We also checked references in the papers we found. The results of
183 this search are summarized in the Introduction.

184 In the results of the UK Biobank GWAS for hand preference, we first checked the p-values for
185 association, for each of the specific SNPs reported in the previous papers (Table 1). We also
186 generated association scores for each individual gene implicated in the previous papers, by use of the
187 Magma program as implemented in the FUMA package v1.3.3 (see Supp. Table 1 for specific settings)
188 [50](August 2018). These gene-based scores summarize the overall level of association at all SNPs
189 spanning a given gene, into one single score and corresponding P value.

190

191 Gene-sets involved in visceral laterality

192 To test for the involvement of genes associated with visceral asymmetry in relative hand skill,
193 Brandler et al. had selected a number of mouse phenotypes related to visceral asymmetry (see
194 Introduction), such as 'dextrocardia' and 'situs inversus', from all those available in the Mouse
195 Genome Informatics (MGI) resource (http://www.informatics.jax.org/). In this database, mutations in
196 specific genes have been linked to resulting phenotypes, such that each phenotype has a set of
197 individual genes annotated to it. The exact criteria by which Brandler et al. selected their specific
198 phenotypes for analysis were not described. In addition, new relevant mouse laterality phenotypes,
199 and their associated genes, may have been added since 2013. We therefore made an up-to-date
200 selection of phenotypes related to visceral asymmetry in the MGI, in the following way: In the
201 hierarchical tree for mouse phenotypes (http://www.informatics.jax.org/vocab/mp_ontology, MGI
202 6.12, last updated 06/19/2018), we searched for 'heterotaxy', 'situs inversus', 'isomerism' and
203 'dextrocardia', and also included all child terms if they also related to asymmetry phenotypes. We
204 only included terms with at least 15 genes. This approach resulted in a list of 11 mouse phenotypes
205 (See Results). The mouse genes were then mapped to corresponding human genes, using

206 homologene.data (v68, May 2014) from ftp://ftp.ncbi.nih.gov/pub/HomoloGene/current, by
207 matching mouse genes with human genes that had the same HID (HomoloGene group identifier). The
208 list of phenotypes and the associated human genes can be found in Supplementary Table 2.

209 In the Online Mendelian Inheritance in Man database OMIM (https://omim.org/, last updated on 26
210 Jun 2018), we also identified all genes in the human phenotypic series 'Primary Ciliary Dyskinesia'
211 (MIM # 244400), because half of the patients with this disorder present with situs inversus. These
212 genes were used to form one additional gene-set, thus in this study we tested a total of twelve sets,
213 eleven from the mouse database and one based directly on human genetics (See Results).

214

215 Seven of our mouse phenotypes were among those previously analysed by Brandler et al. (Supp.
216 Table 3). We also repeated our analyses using the exact same list of mouse phenotypes used by
217 Brandler et al. (Supp. Table 3). However, the gene lists associated with each mouse phenotype may
218 have changed since Brandler et al. performed their study five years ago, as new information on genes
219 affecting visceral asymmetry can have been incorporated.

220 Gene-set enrichment analysis

221 We ran three different gene-set enrichment algorithms that have been developed for application to
222 GWAS results. Brandler et al., in their investigation of gene sets involved in visceral laterality, had
223 used MAGENTA [51]. For consistency we also used MAGENTA (v2, 21 July 2011), plus two newer
224 algorithms called Magma ([52], v1.06) and Pascal ([53](no version number). The three enrichment
225 algorithms work in different ways, but essentially they first assign a single association score to each
226 genes based on the GWAS data, and then test whether the genes in a given set show, on average,
227 more evidence for association with the trait in question than the rest of the genes in the genome for
228 which scores could be calculated (hence these are sometimes called 'competitive' analyses [54]),
229 while accounting for non-independence of SNPs due to linkage disequilibrium. For Magma and
230 Pascal, we used default settings, while for MAGENTA we chose the settings as used by Brandler *et al.*
231 (parameter settings for all analyses can be found in Supp. Table 1). Pascal and Magma offered the
232 option to calculate gene-scores based on the single most associated SNP within a gene (the 'max'
233 option), or on a combination of SNPs within the gene (the 'sum' option), and we ran both approaches
234 with both softwares, for an exhaustive assessment of whether the previously implicated gene sets in
235 the literature might affect handedness in the UK Biobank.

236

Results

As expected, the GWAS for right-handedness vs non-right-handedness in the UK Biobank dataset was very similar to the earlier reported GWAS for left-handedness vs non-left-handedness in this dataset [49, 55](see also http://big.stats.ox.ac.uk/pheno/biobank_1707_2). On chromosome 2, the SNP rs13017199, upstream of the gene *MAP2*, was most significantly associated with non-right-handedness (p=9.4E-10). On chromosome 17, rs1615553 was most significantly associated (p=3.6E-09), but as this region has unusually extended linkage disequilibrium, then any one of the following genes are among the positional candidates*: PLEKHM1, CRHR1, SPPL2C, MAPT, STH, KANSL1, ARL17B, LRRC37A, LRRC37A2, ARL17A, NSF,* and *WNT3*. The loci on chromosomes 2 and 17 showed no hint of association in the analysis of ambidextrous vs non-ambidextrous people (p=0.70 and p=0.54 for rs13017199 and rs1615553, respectively).

None of the SNPs previously reported in the literature, in datasets other than the UK Biobank itself (see Introduction), had a significant effect on non-right-handedness in the UK Biobank (Table 1). Nor was there any effect at the gene-level, for any of the previously reported genes (Table 1). Also for the trait definitions of 'ambidextrous vs other' and 'left-handed vs other', none of the previously claimed SNPs from other datasets showed significant association in the UK Biobank (Table 1), even though some of the previous reports had involved measures of the degree of hand dominance rather than its direction.

Table 1 Significance of association with hand preference measures of previous findings.

GENE	CHR	START (BP, GRHC37)	END (BP, GRHC37)	SNP	P-GENE RIGHT[a]	P-SNP RIGHT[a]	P-SNP LEFT[b]	P-SNP AMBI[c]	MAIN REFERENCE
LRRTM1	2	80515483	80531874	rs1007371	0.78	0.76	0.55	0.53	[31]
PCSK6	15	101840818	102065405	rs7182874	0.82	0.63	0.78	0.58	[43]
COMT	22	19929130	19957498	rs4680	0.84	0.76	0.62	0.69	[36]
SETDB2	13	50018429	50069138	rs4942830	0.81	0.89	0.42	0.14	[39]
SCN11A	3	38887260	38992052	rs883565	0.60	0.56	0.73	0.53	[25]
AK3	9	4711155	4742043	rs296859	0.88	0.39	0.28	0.65	[25]
AR	X	66764465	66950461	micro-satellites[d]	0.79	-	-	-	[33]

Significance of association with hand preference measures in the UKBiobank, for SNPs and genes previously implicated in the literature. Gene-level association is shown for the right-handed versus non-righthanded phenotype, and SNP level association for all three hand preference contrasts.

[a] RIGHT: using GWAS of right-handed vs non-right-handed.

[b] LEFT: using GWAS of left-handed vs non-left-handed.

[c] AMBI: using GWAS of ambidextrous vs non-ambidextrous.

[d] The original study made use of a microsatellite repeat polymorphism which was not genotyped or imputed in the UK Biobank dataset.

None of the gene-set enrichment analyses supported the proposition that sets related to visceral asymmetry are particularly associated with non-right-handedness (Table 2, Supp. Table 3).

Table 2 Gene set enrichment results for visceral asymmetry-related gene-sets.

MOUSE ID	DESCRIPTION	PASCAL SUM P	PASCAL MAX P	MAGMA SUM P	MAGMA MAX P	MAGENTA P
MP:0000508	right-sided isomerism	0.64	0.87	0.15	0.11	0.34
MP:0000531	right pulmonary isomerism	0.52	0.71	0.32	0.34	0.69
MP:0000542	left-sided isomerism	0.54	0.60	0.47	0.69	0.30
MP:0000644	dextrocardia	0.22	0.75	0.35	0.20	0.37
MP:0001706	abnormal left-right axis patterning	0.58	0.76	0.64	0.19	0.51
MP:0002766	situs inversus	0.23	0.19	0.62	0.44	0.34
MP:0003178	left pulmonary isomerism	0.64	0.60	0.69	0.71	0.36
MP:0004133	heterotaxia	0.22	0.65	0.01	0.27	0.05
MP:0010808	right-sided stomach	0.08	0.11	0.62	0.04	0.17
MP:0011250	abdominal situs ambiguus	0.01	0.12	0.50	0.31	0.06
MP:0011252	situs inversus totalis	0.16	0.30	0.39	0.40	0.13
PCD	human primary ciliary dyskinesia	0.36	0.38	0.35	0.08	0.30

Gene set enrichment results for visceral asymmetry-related gene-sets, based on the UK Biobank GWAS for non-right-handedness versus right-handedness, and using different softwares and settings. See Supplementary Table 1 for the settings. The uncorrected P values for each gene set and enrichment analysis are shown. None would survive correction for multiple testing.

Discussion

In a very large dataset comprising hundreds of thousands of adult subjects from the general population, we found no evidence for an involvement in hand preference of any genetic variants, genes, or gene-sets that have been previously claimed in the literature. We consider the most likely explanation to be that the earlier findings were false positives, as the study sample sizes were orders of magnitude smaller than the present analysis (see Introduction). However, as the earlier studies

282 used various different trait measures related to handedness, and some made use of selected
283 disorder populations, then it remains possible that some of the earlier findings were indeed real, but
284 not detectable in the present analysis (see Introduction).

285 There was no evidence for an involvement, in hand preference, of common variants in genes related
286 to visceral left-right patterning. Note that Brandler et al. [43] performed analysis of a quantitative
287 handedness index based on peg moving, and included a sample with reading disability, when they
288 originally reported such a relationship. Our present analysis was not an attempt to directly replicate
289 the study of Brandler *et al.*, but rather it was a related investigation, of genes involved in visceral
290 asymmetry with respect to questionnaire-defined, binary-trait hand preference, in a large dataset
291 from the general population. In the rare genetic disorder Primary Ciliary Dyskinesia (PCD)(MIM #
292 244400), recessive mutations in specific genes involved in ciliary biology result in a 50% chance of
293 mirror-reversed left-right visceral asymmetry, a condition known as *situs inversus totalis (*SIT) [56].
294 When PCD and SIT co-occur (the combination is known as Kartagener syndrome), it appears that the
295 rate of left-handedness is unchanged from the general population [57]. However, there may be an
296 increase of left-handedness in people with SIT when they do not have PCD [58, 59], which would
297 suggest the existence of some developmental mechanisms which link visceral asymmetry with brain
298 asymmetry. Nonetheless, a recent genome-wide mutation screening study did not identify any
299 individual genes as likely candidates to cause non-PCD SIT when accompanied by left-handedness
300 [60], and it is possible that the aetiology is multifactorial or even non-genetic [60, 61]. At present, the
301 study by Brandler et al. remains the only one to report tentative evidence for a molecular genetic link
302 between visceral laterality and handedness.

303 As already noted, only two loci were found associated with non-right-handedness in the UK Biobank
304 GWAS. The most likely causative gene within the large chromosome 17 inversion cannot be
305 determined on the basis of these data, as the region spans at least twelve genes showing similar
306 levels of association with the trait. This region shows association with various other human traits (see
307 e.g. http://big.stats.ox.ac.uk/variant/17-44515243-C-T). For the locus on chromosome 2, the most
308 probable gene appears to be *MAP2*: the association signal extends from upstream into this gene's
309 coding region, and the single most associated SNP is associated with expression differences of *MAP2*
310 in oesophageal tissue, according to the GTeX database (https://www.gtexportal.org/home/ Release
311 V7 (dbGaP Accession phs000424.v7.p2)), and not with any other gene's expression level. MAP2
312 protein is a well-known marker for neuronal cells, and specifically the perikarya and dendrites of
313 these cells [62]. MAP2 is involved in neurogenesis [63], and almost exclusively expressed in the brain
314 [64]. The protein plays a role during the development of various brain structures (e.g. [65, 66]), and
315 in mice seems to play a role in motor skills [67]. One report suggested that *MAP2* is more highly

316 expressed in right hippocampus than left during development in the rat [68]. How exactly this gene
317 may act in affecting motor laterality in human development remains unknown, but we speculate on
318 the basis of its known functions that it is a downstream effector of lateralized development, rather
319 than a primary creator of left-right laterality. Regardless, as the genetic association is based on
320 hundreds of thousands of study participants, *MAP2* must be considered the single most reliably
321 implicated gene in human hand preference yet identified. However, replication is desired.

322

323 There may have been some particular sources of noise in the UK Biobank definitions of hand
324 preference. An earlier analysis of the UK biobank dataset [26] suggested a reduction in left-hand
325 preference of roughly 20% among the oldest participants (born around 1940), relative to younger
326 participants (born around 1970), which suggests that some of the older left-handed people were
327 forced to switch to right-handedness during childhood. The GWAS analysis did, however, adjust for
328 age as a covariate effect. In addition, the location of birth within the UK was found to influence the
329 probability of being left-handed [26], likely primarily for cultural rather than biological reasons. The
330 ambidextrous group was also found to give a high rate of inconsistent answers between different
331 assessment visits [26].

332 It is striking that common genetic variants in the UK Biobank dataset have little overall effect on hand
333 preference, as measured by a very low SNP-based heritability (only 2-3%)[48, 69], while previous
334 twin-based studies have indicated a heritability of roughly 25% for left-hand preference (see
335 Introduction). It has been noted before that behavioural traits can show a particularly large
336 difference between twin and SNP-based heritability estimates [70]. A commonly given explanation is
337 that much of the heritability may be due to rare SNPs and mutations, which are not well captured by
338 genotyping arrays and imputation protocols in GWAS studies. Rare mutations can be relatively recent
339 in origin, and under negative selection. Whether these possibilities apply to hand preference will
340 need to be investigated in future large-scale genome sequencing studies.

341

342 Conclusion

343 In conclusion, previously reported genetic associations with measures related to handedness, found
344 in datasets other than the UK biobank, were not supported by analysis of this very large cohort. We
345 also found no supportive evidence that common variants within genes involved in visceral left-right
346 patterning contribute to hand preference. We consider the most likely explanation for the
347 discrepancy to be that the previous findings were noise, which arose from limited sample sizes.
348 Differences of trait measurement and population selection might also be involved. Regardless, what

is known of the molecular genetic basis of hand preference remains tentative and extremely limited, with the gene *MAP2* providing the most robust lead so far.

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References

1. Gilbert AN, Wysocki CJ. Hand preference and age in the United States. Neuropsychologia. 1992;30(7):601-8. PubMed PMID: 1528408.

2. Hepper PG, Wells DL, Lynch C. Prenatal thumb sucking is related to postnatal handedness. Neuropsychologia. 2005;43(3):313-5. doi: 10.1016/j.neuropsychologia.2004.08.009. PubMed PMID: 15707608.

3. Hepper PG. The developmental origins of laterality: Fetal handedness. Developmental Psychobiology. 2013;55(6):588-95. doi: 10.1002/dev.21119. PubMed PMID: 23765736.

4. Parma V, Brasselet R, Zoia S, Bulgheroni M, Castiello U. The origin of human handedness and its role in pre-birth motor control. Sci Rep. 2017;7(1):16804. Epub 2017/12/03. doi: 10.1038/s41598-017-16827-y. PubMed PMID: 29196664; PubMed Central PMCID: PMCPMC5711880.

5. Scharoun SM, Bryden PJ. Hand preference, performance abilities, and hand selection in children. Front Psychol. 2014;5:82. Epub 2014/03/07. doi: 10.3389/fpsyg.2014.00082. PubMed PMID: 24600414; PubMed Central PMCID: PMCPMC3927078.

6. de Kovel CGF, Lisgo S, Karlebach G, Ju J, Cheng G, Fisher SE, et al. Left-Right Asymmetry of Maturation Rates in Human Embryonic Neural Development. Biol Psychiatry. 2017;82(3):204-12. doi: 10.1016/j.biopsych.2017.01.016. PubMed PMID: 28267988.

375 7. de Kovel CGF, Lisgo SN, Fisher SE, Francks C. Subtle left-right asymmetry of gene expression
376 profiles in embryonic and foetal human brains. Sci Rep-Uk. 2018;8(1):12606. doi: 10.1038/s41598-
377 018-29496-2.
378 8. Faurie C, Raymond M. Handedness frequency over more than ten thousand years. Proc Biol
379 Sci. 2004;271 Suppl 3:S43-5. Epub 2004/04/23. doi: 10.1098/rsbl.2003.0092. PubMed PMID:
380 15101415; PubMed Central PMCID: PMCPMC1809976.
381 9. Coren S, Porac C. Fifty centuries of right-handedness: the historical record. Science.
382 1977;198(4317):631-2. Epub 1977/11/11. PubMed PMID: 335510.
383 10. Medland SE, Perelle I, Monte VD, Ehrman L. Effects of culture, sex, and age on the
384 distribution of handedness: An evaluation of the sensitivity of three measures of handedness.
385 Laterality. 2004;9(3):287-97. doi: 10.1080/13576500342000040. PubMed PMID: 13105049.
386 11. Raymond M, Pontier D. Is there geographical variation in human handedness? Laterality.
387 2004;9(1):35-51. Epub 2004/09/24. doi: 10.1080/13576500244000274. PubMed PMID: 15382729.
388 12. Francks C. Exploring human brain lateralization with molecular genetics and genomics.
389 Annals of the New York Academy of Sciences. 2015;1359(1):1-13. doi: 10.1111/nyas.12770. PubMed
390 PMID: 25950729.
391 13. Duboc V, Dufourcq P, Blader P, Roussigne M. Asymmetry of the Brain: Development and
392 Implications. Annu Rev Genet. 2015;49:647-72. doi: 10.1146/annurev-genet-112414-055322.
393 PubMed PMID: 26442849.
394 14. Sun T, Walsh CA. Molecular approaches to brain asymmetry and handedness. Nature
395 Reviews Neuroscience. 2006;7:655. doi: 10.1038/nrn1930.
396 15. Corballis MC. Left brain, right brain: facts and fantasies. PLoS biology. 2014;12(1):e1001767.
397 Epub 2014/01/28. doi: 10.1371/journal.pbio.1001767. PubMed PMID: 24465175; PubMed Central
398 PMCID: PMCPMC3897366.

399 16. Vuoksimaa E, Koskenvuo M, Rose RJ, Kaprio J. Origins of handedness: A nationwide study of
400 30161 adults. Neuropsychologia. 2009;47(5):1294-301. doi:
401 https://doi.org/10.1016/j.neuropsychologia.2009.01.007.
402 17. Medland SE, Duffy DL, Wright MJ, Geffen GM, Hay DA, Levy F, et al. Genetic influences on
403 handedness: data from 25,732 Australian and Dutch twin families. Neuropsychologia.
404 2009;47(2):330-7. doi: 10.1016/j.neuropsychologia.2008.09.005. PubMed PMID: 18824185; PubMed
405 Central PMCID: PMCPMC2755095.
406 18. Medland SE, Duffy DL, Wright MJ, Geffen GM, Martin NG. Handedness in twins: joint analysis
407 of data from 35 samples. Twin Res Hum Genet. 2006;9(1):46-53. doi: 10.1375/183242706776402885.
408 PubMed PMID: 16611467.
409 19. Suzuki K, Ando J. Genetic and environmental structure of individual differences in hand, foot,
410 and ear preferences: A twin study. Laterality: Asymmetries of Body, Brain and Cognition.
411 2014;19(1):113-28. doi: 10.1080/1357650X.2013.790396.
412 20. McManus IC. Handedness, language dominance and aphasia: a genetic model. Psychological
413 medicine Monograph supplement. 1985;8:1-40. Epub 1985/01/01. PubMed PMID: 3863155.
414 21. Annett M. Handedness and Cerebral Dominance. The Journal of Neuropsychiatry and Clinical
415 Neurosciences. 1998;10(4):459-69. doi: 10.1176/jnp.10.4.459. PubMed PMID: 9813794.
416 22. Kavaklioglu T, Ajmal M, Hameed A, Francks C. Whole exome sequencing for handedness in a
417 large and highly consanguineous family. Neuropsychologia. 2016;93(Pt B):342-9. Epub 2015/11/20.
418 doi: 10.1016/j.neuropsychologia.2015.11.010. PubMed PMID: 26581626.
419 23. Somers M, Ophoff RA, Aukes MF, Cantor RM, Boks MP, Dauwan M, et al. Linkage analysis in a
420 Dutch population isolate shows no major gene for left-handedness or atypical language
421 lateralization. J Neurosci. 2015;35(23):8730-6. doi: 10.1523/JNEUROSCI.3287-14.2015. PubMed
422 PMID: 26063907; PubMed Central PMCID: PMCPMC4589567.

423 24. Warren DM, Stern M, Duggirala R, Dyer TD, Almasy L. Heritability and linkage analysis of
424 hand, foot, and eye preference in Mexican Americans. Laterality. 2006;11(6):508-24. Epub
425 2006/09/13. doi: 10.1080/13576500600761056. PubMed PMID: 16966240.
426 25. Armour JA, Davison A, McManus IC. Genome-wide association study of handedness excludes
427 simple genetic models. Heredity (Edinb). 2014;112(3):221-5. doi: 10.1038/hdy.2013.93. PubMed
428 PMID: 24065183; PubMed Central PMCID: PMCPMC3931166.
429 26. de Kovel CGF, Carrion-Castillo A, Francks C. A large-scale population study of early life factors
430 influencing left-handedness. bioRxiv. 2018. doi: 10.1101/305425.
431 27. Johnston DW, Nicholls MER, Shah MA, Shields MA. Handedness, Health and Cognitive
432 Development: Evidence from Children in the NLSY. Bonn, Germany: Forschungsinstitut zur Zukunft
433 der Arbeit, 2010 Contract No.: No. 4774.
434 28. Annett M, Turner A. Laterality and the growth of intellectual abilities. British Journal of
435 Educational Psychology. 1974;44(1):37-46. doi: doi:10.1111/j.2044-8279.1974.tb00764.x.
436 29. Francks C, Fisher SE, MacPhie IL, Richardson AJ, Marlow AJ, Stein JF, et al. A Genomewide
437 Linkage Screen for Relative Hand Skill in Sibling Pairs. The American Journal of Human Genetics.
438 2002;70(3):800-5. doi: https://doi.org/10.1086/339249.
439 30. Francks C, DeLisi LE, Shaw SH, Fisher SE, Richardson AJ, Stein JF, et al. Parent-of-origin effects
440 on handedness and schizophrenia susceptibility on chromosome 2p12–q11. Human Molecular
441 Genetics. 2003;12(24):3225-30. doi: 10.1093/hmg/ddg362.
442 31. Francks C, Maegawa S, Laurén J, Abrahams BS, Velayos-Baeza A, Medland SE, et al. LRRTM1
443 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness
444 and schizophrenia. Molecular Psychiatry. 2007;12:1129. doi: 10.1038/sj.mp.4002053
445 https://www.nature.com/articles/4002053#supplementary-information.
446 32. Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations,
447 and pathology: I. A hypothesis and a program for research. Archives of neurology. 1985;42(5):428-59.
448 Epub 1985/05/01. PubMed PMID: 3994562.

449 33. Medland SE, Duffy DL, Spurdle AB, Wright MJ, Geffen GM, Montgomery GW, et al. Opposite
450 effects of androgen receptor CAG repeat length on increased risk of left-handedness in males and
451 females. Behav Genet. 2005;35(6):735-44. Epub 2005/11/08. doi: 10.1007/s10519-005-6187-3.
452 PubMed PMID: 16273319.
453 34. Arning L, Ocklenburg S, Schulz S, Ness V, Gerding WM, Hengstler JG, et al. Handedness and
454 the X chromosome: the role of androgen receptor CAG-repeat length. Sci Rep. 2015;5:8325. Epub
455 2015/02/11. doi: 10.1038/srep08325. PubMed PMID: 25659367; PubMed Central PMCID:
456 PMCPMC4321186.
457 35. Hampson E, Sankar JS. Hand preference in humans is associated with testosterone levels and
458 androgen receptor gene polymorphism. Neuropsychologia. 2012;50(8):2018-25. Epub 2012/05/15.
459 doi: 10.1016/j.neuropsychologia.2012.04.027. PubMed PMID: 22579704.
460 36. Savitz J, van der Merwe L, Solms M, Ramesar R. Lateralization of hand skill in bipolar affective
461 disorder. Genes Brain Behav. 2007;6(8):698-705. Epub 2007/02/21. doi: 10.1111/j.1601-
462 183X.2006.00299.x. PubMed PMID: 17309660.
463 37. Maier W, Hofgen B, Zobel A, Rietschel M. Genetic models of schizophrenia and bipolar
464 disorder: overlapping inheritance or discrete genotypes? European archives of psychiatry and clinical
465 neuroscience. 2005;255(3):159-66. Epub 2005/07/05. doi: 10.1007/s00406-005-0583-9. PubMed
466 PMID: 15995899.
467 38. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory.
468 Neuropsychologia. 1971;9(1):97-113. doi: https://doi.org/10.1016/0028-3932(71)90067-4.
469 39. Ocklenburg S, Arning L, Gerding WM, Hengstler JG, Epplen JT, Gunturkun O, et al. Left-Right
470 Axis Differentiation and Functional Lateralization: a Haplotype in the Methyltransferase Encoding
471 Gene SETDB2 Might Mediate Handedness in Healthy Adults. Molecular neurobiology.
472 2016;53(9):6355-61. Epub 2016/11/01. doi: 10.1007/s12035-015-9534-2. PubMed PMID: 26572639.
473 40. Crespi B, Read S, Hurd P. The SETDB2 locus: evidence for a genetic link between handedness
474 and atopic disease. Heredity. 2018;120(1):77-82. doi: 10.1038/s41437-017-0004-7.

475 41. Xu PF, Zhu KY, Jin Y, Chen Y, Sun XJ, Deng M, et al. Setdb2 restricts dorsal organizer territory
476 and regulates left-right asymmetry through suppressing fgf8 activity. Proc Natl Acad Sci U S A.
477 2010;107(6):2521-6. Epub 2010/02/06. doi: 10.1073/pnas.0914396107. PubMed PMID: 20133783;
478 PubMed Central PMCID: PMCPMC2823908.
479 42. Scerri TS, Brandler WM, Paracchini S, Morris AP, Ring SM, Richardson AJ, et al. PCSK6 is
480 associated with handedness in individuals with dyslexia. Human Molecular Genetics. 2011;20(3):608-
481 14. doi: 10.1093/hmg/ddq475.
482 43. Brandler WM, Morris AP, Evans DM, Scerri TS, Kemp JP, Timpson NJ, et al. Common variants
483 in left/right asymmetry genes and pathways are associated with relative hand skill. PLoS Genet.
484 2013;9(9):e1003751. doi: 10.1371/journal.pgen.1003751. PubMed PMID: 24068947; PubMed Central
485 PMCID: PMCPMC3772043.
486 44. Eriksson N, Macpherson JM, Tung JY, Hon LS, Naughton B, Saxonov S, et al. Web-based,
487 participant-driven studies yield novel genetic associations for common traits. PLoS Genet.
488 2010;6(6):e1000993. Epub 2010/06/30. doi: 10.1371/journal.pgen.1000993. PubMed PMID:
489 20585627; PubMed Central PMCID: PMCPMC2891811 and own stock options in the company.
490 23andMe co-president AW has provided general guidance, including guidance related to the
491 company's research undertakings and direction. PLoS Genetics' Editor-in-Chief Gregory S. Barsh is a
492 potential consultant to 23andMe and therefore recused himself from the editorial and peer-review
493 process. PLoS co-founder Michael B. Eisen is a member of the 23andMe Scientific Advisory Board.
494 45. Ku CS, Loy EY, Pawitan Y, Chia KS. The pursuit of genome-wide association studies: where are
495 we now? Journal of human genetics. 2010;55(4):195-206. Epub 2010/03/20. doi:
496 10.1038/jhg.2010.19. PubMed PMID: 20300123.
497 46. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why
498 small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.
499 Epub 2013/04/11. doi: 10.1038/nrn3475. PubMed PMID: 23571845.

500 47. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access
501 resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS
502 medicine. 2015;12(3):e1001779. Epub 2015/04/01. doi: 10.1371/journal.pmed.1001779. PubMed
503 PMID: 25826379; PubMed Central PMCID: PMCPMC4380465.
504 48. Neale B. Heritability of >2,000 traits and disorders in the UK Biobank 2017. Available from:
505 http://www.nealelab.is/blog/2017/9/15/heritability-of-2000-traits-and-disorders-in-the-uk-biobank.
506 49. Rapid GWAS of thousands of phenotypes for 337,000 samples in the UK Biobank [Internet].
507 2017. Available from: http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-
508 phenotypes-for-337000-samples-in-the-uk-biobank.
509 50. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation
510 of genetic associations with FUMA. Nature Communications. 2017;8(1):1826. doi: 10.1038/s41467-
511 017-01261-5.
512 51. Segrè AV, Diagram Consortium, Magic investigators, Groop L, Mootha VK, Daly MJ, et al.
513 Common Inherited Variation in Mitochondrial Genes Is Not Enriched for Associations with Type 2
514 Diabetes or Related Glycemic Traits. PLOS Genetics. 2010;6(8):e1001058. doi:
515 10.1371/journal.pgen.1001058.
516 52. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: Generalized Gene-Set Analysis of
517 GWAS Data. PLoS computational biology. 2015;11(4):e1004219. doi: 10.1371/journal.pcbi.1004219.
518 53. Lamparter D, Marbach D, Rueedi R, Kutalik Z, Bergmann S. Fast and Rigorous Computation of
519 Gene and Pathway Scores from SNP-Based Summary Statistics. PLoS computational biology.
520 2016;12(1):e1004714. doi: 10.1371/journal.pcbi.1004714. PubMed PMID: 26808494; PubMed
521 Central PMCID: PMC4726509.
522 54. Evangelou M, Rendon A, Ouwehand WH, Wernisch L, Dudbridge F. Comparison of methods
523 for competitive tests of pathway analysis. PLoS One. 2012;7(7):e41018. Epub 2012/08/04. doi:
524 10.1371/journal.pone.0041018. PubMed PMID: 22859961; PubMed Central PMCID:
525 PMCPMC3409204.

526 55. Canela-Xandri O, Rawlik K, Tenesa A. An atlas of genetic associations in UK Biobank. bioRxiv.
527 2017. doi: 10.1101/176834.
528 56. Deng H, Xia H, Deng S. Genetic basis of human left-right asymmetry disorders. Expert Rev
529 Mol Med. 2015;16:e19. Epub 2015/08/11. doi: 10.1017/erm.2014.22. PubMed PMID: 26258520.
530 57. McManus IC, Martin N, Stubbings GF, Chung EM, Mitchison HM. Handedness and situs
531 inversus in primary ciliary dyskinesia. Proc Biol Sci. 2004;271(1557):2579-82. doi:
532 10.1098/rspb.2004.2881. PubMed PMID: 15615683; PubMed Central PMCID: PMCPMC1691902.
533 58. Vingerhoets G, Li X, Hou L, Bogaert S, Verhelst H, Gerrits R, et al. Brain structural and
534 functional asymmetry in human situs inversus totalis. Brain Struct Funct. 2018;223(4):1937-52. Epub
535 2018/01/06. doi: 10.1007/s00429-017-1598-5. PubMed PMID: 29302744.
536 59. Vingerhoets G, Gerrits R, Bogaert S. Atypical brain functional segregation is more frequent in
537 situs inversus totalis. Cortex. 2018;106:12-25. doi: 10.1016/j.cortex.2018.04.012. PubMed PMID:
538 29864592.
539 60. Postema MC, Carrion-Castillo A, Fisher SE, Vingerhoets G, Francks C. The genetics of situs
540 inversus totalis without primary ciliary dyskinesia. bioRxiv. 2018. doi: 10.1101/422964.
541 61. Aylsworth AS. Clinical aspects of defects in the determination of laterality. American Journal
542 of Medical Genetics. 2001;101(4):345-55. doi: doi:10.1002/ajmg.1219.
543 62. Caceres A, Binder LI, Payne MR, Bender P, Rebhun L, Steward O. Differential subcellular
544 localization of tubulin and the microtubule-associated protein MAP2 in brain tissue as revealed by
545 immunocytochemistry with monoclonal hybridoma antibodies. J Neurosci. 1984;4(2):394-410. Epub
546 1984/02/01. PubMed PMID: 6699682.
547 63. Harada A, Teng J, Takei Y, Oguchi K, Hirokawa N. MAP2 is required for dendrite elongation,
548 PKA anchoring in dendrites, and proper PKA signal transduction. The Journal of Cell Biology.
549 2002;158(3):541-9. doi: 10.1083/jcb.200110134.
550 64. Fagerberg L, Hallstrom BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, et al. Analysis of
551 the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-

552 based proteomics. Molecular & cellular proteomics : MCP. 2014;13(2):397-406. Epub 2013/12/07.
553 doi: 10.1074/mcp.M113.035600. PubMed PMID: 24309898; PubMed Central PMCID:
554 PMCPMC3916642.
555 65. Martin-Lopez E, Meller SJ, Greer CA. Development of piriform cortex interhemispheric
556 connections via the anterior commissure: progressive and regressive strategies. Brain Struct Funct.
557 2018. Epub 2018/08/25. doi: 10.1007/s00429-018-1741-y. PubMed PMID: 30141078.
558 66. Blumcke I, Becker AJ, Normann S, Hans V, Riederer BM, Krajewski S, et al. Distinct expression
559 pattern of microtubule-associated protein-2 in human oligodendrogliomas and glial precursor cells.
560 Journal of neuropathology and experimental neurology. 2001;60(10):984-93. Epub 2001/10/09.
561 PubMed PMID: 11589429.
562 67. Tamakoshi K, Kawanaka K, Onishi H, Takamatsu Y, Ishida K. Motor Skills Training Improves
563 Sensorimotor Dysfunction and Increases Microtubule-Associated Protein 2 mRNA Expression in Rats
564 with Intracerebral Hemorrhage. Journal of stroke and cerebrovascular diseases : the official journal
565 of National Stroke Association. 2016;25(8):2071-7. Epub 2016/06/07. doi:
566 10.1016/j.jstrokecerebrovasdis.2016.05.007. PubMed PMID: 27265094.
567 68. Moskal JR, Kroes RA, Otto NJ, Rahimi O, Claiborne BJ. Distinct patterns of gene expression in
568 the left and right hippocampal formation of developing rats. Hippocampus. 2006;16(8):629-34. Epub
569 2006/07/19. doi: 10.1002/hipo.20198. PubMed PMID: 16847945.
570 69. Ge T, Chen CY, Neale BM, Sabuncu MR, Smoller JW. Phenome-wide heritability analysis of
571 the UK Biobank. PLoS Genet. 2017;13(4):e1006711. doi: 10.1371/journal.pgen.1006711. PubMed
572 PMID: 28388634; PubMed Central PMCID: PMCPMC5400281.
573 70. Cheesman R, Selzam S, Ronald A, Dale PS, McAdams TA, Eley TC, et al. Childhood behaviour
574 problems show the greatest gap between DNA-based and twin heritability. Transl Psychiatry.
575 2017;7(12):1284. Epub 2017/12/14. doi: 10.1038/s41398-017-0046-x. PubMed PMID: 29234009;
576 PubMed Central PMCID: PMCPMC5802501.

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580 # Supplemental Information docx

581 Supp. Table 1: Software packages and settings for the various analyses.

582 Supp. Table 3: Results for visceral asymmetry-related gene-sets as used in the previous analysis by
583 Brandler *et al.* (2013)

584

585 # Supplemental table excel

586 Supp. Table 2 GMT-formatted gene-sets used in the current study. Entrez identifiers.

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