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 have been reported to associate with hand preference or quantitative measures related to it, 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 at the whole gene-level for any of 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 indicate 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 a broad region on chromosomes 2 [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 17q21
137 and spans many genes, while the other was close to the gene *MAP2* (Microtubule Associated Protein
138 2) on chromosome 2q34. However, there may be other loci which are truly associated with hand
139 preference in the UK Biobank GWAS results, but which do not reach the threshold of significance to
140 survive correction for multiple testing over the whole genome (i.e. roughly $P=5x10^{-8}$). SNP-based
141 heritability analysis, based on variation over all of the autosomes (i.e. all chromosomes minus the sex
142 chromosomes) arrived at explained variance (SNP-heritability) for left-handedness of only 1.8% in the

143 UK Biobank (p=6.4e-03), which is markedly lower than previous indications from twin studies (see
144 above), while ambidexterity 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 'Other' does not include the handful of people who ticked 'prefer not to say'. Heritability estimates
163 as reported above were based on this release. Samples were genetically independent and of white
164 British ancestry [48]. GWAS results were also available from a second release (August 2018,
165 http://www.nealelab.is/uk-biobank/) on 361,194 subjects. This second release included more
166 individuals, updated genotype data, and the addition of the X-chromosome, as well as additional
167 covariates for the association analysis, among which were age and age^2. The analysed traits now also
168 included 'right-handed vs other' (40,671 right-handers vs 320,242 non-right-handers, i.e.
169 ambidextrous individuals were now combined with the left-handers). This is the trait (1707.1) that
170 we predominantly used in the present study for our analyses (below), but we also include look-ups of
171 previously reported candidate SNPs in relation to the 'left-handed versus other' (34,585 cases) and
172 'ambidextrous versus other' (6,086 cases) results. The GWAS for ambidexterity was necessarily based
173 on a smaller sample size in the 'case' group than the other trait definitions, and accordingly the
174 power would have been lower.

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

178 Previously implicated SNPs and genes

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

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

192

193 Gene-sets involved in visceral laterality

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

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

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

216

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

222 Gene-set enrichment analysis

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

238

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 2q34, the SNP rs13017199, upstream of the gene *MAP2*, was most significantly associated with non-right-handedness (p=9.4E-10, minor allele frequency 0.34, beta for right-handedness for C-allele= -0.005). On chromosome 17q21, rs1615553 was most significantly associated (p=3.6E-09, minor allele frequency 0.30, beta for right-handedness for G-allele=0.005), 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*. These 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 whole-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 UK Biobank, for SNPs and genes previously implicated in the literature. Gene-level association is shown for the right-handed versus non-right-handed 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,

283 genes, or gene-sets that have been previously claimed in the literature. We consider the most likely
284 explanation to be that the earlier findings were false positives, as the study sample sizes were orders
285 of magnitude smaller than the present analysis (see Introduction). However, as the earlier studies
286 used various different trait measures related to handedness, and some made use of selected
287 disorder populations, then it remains possible that some of the earlier findings were indeed real, but
288 not detectable in the present analysis (see Introduction).

289 There was no evidence for an involvement, in hand preference, of common variants in genes related
290 to visceral left-right patterning. Note that Brandler et al. [43] performed analysis of a quantitative
291 handedness index based on peg moving, and included a sample with reading disability, when they
292 originally reported such a relationship. Our present analysis was not an attempt to directly replicate
293 the study of Brandler *et al.*, but rather it was a related investigation, of genes involved in visceral
294 asymmetry with respect to questionnaire-defined, binary-trait hand preference, in a large dataset
295 from the general population. In the rare genetic disorder Primary Ciliary Dyskinesia (PCD)(MIM #
296 244400), recessive mutations in specific genes involved in ciliary biology result in a 50% chance of
297 mirror-reversed left-right visceral asymmetry, a condition known as *situs inversus totalis (*SIT) [56].
298 When PCD and SIT co-occur (the combination is known as Kartagener syndrome), it appears that the
299 rate of left-handedness is unchanged from the general population [57]. However, there may be an
300 increase of left-handedness in people with SIT when they do not have PCD [58, 59], which would
301 suggest the existence of some developmental mechanisms which link visceral asymmetry with brain
302 asymmetry. Nonetheless, a recent genome-wide mutation screening study did not identify any
303 individual genes as likely candidates to cause non-PCD SIT when accompanied by left-handedness
304 [60], and it is possible that the aetiology is multifactorial or even non-genetic [60, 61]. At present, the
305 study by Brandler et al. remains the only one to report tentative evidence for a molecular genetic link
306 between visceral laterality and handedness.

307 As already noted, only two loci were found associated with non-right-handedness in the UK Biobank
308 GWAS. The most likely causative gene within the large chromosome 17q21 inversion cannot be
309 determined on the basis of these data, as the region spans at least twelve genes showing similar
310 levels of association with the trait. This region shows association with various other human traits (see
311 e.g. http://big.stats.ox.ac.uk/variant/17-44515243-C-T). For the locus on chromosome 2q34, the
312 most probable gene appears to be *MAP2*: the association signal extends from upstream into this
313 gene's coding region, and the single most associated SNP is associated with expression differences of
314 *MAP2* in oesophageal tissue, according to the GTeX database (https://www.gtexportal.org/home/
315 Release V7 (dbGaP Accession phs000424.v7.p2)), and not with any other gene's expression level.
316 MAP2 protein is a well-known marker for neuronal cells, and specifically the perikarya and dendrites

317 of these cells [62]. MAP2 is involved in neurogenesis [63], and almost exclusively expressed in the
318 brain [64]. The protein plays a role during the development of various brain structures (e.g. [65, 66]),
319 and in mice seems to play a role in motor skills [67]. One report suggested that *MAP2* is more highly
320 expressed in right hippocampus than left during development in the rat [68]. How exactly this gene
321 may act in affecting motor laterality in human development remains unknown. Regardless, as the
322 genetic association is based on hundreds of thousands of study participants, *MAP2* must be
323 considered the single most reliably implicated gene in human hand preference yet identified.
324 However, replication is desired.

325

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

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

344

345 Conclusion

346 In conclusion, previously reported genetic associations with measures related to handedness, found
347 in datasets other than the UK biobank, were not supported by analysis of this very large cohort. We
348 also found no supportive evidence that common variants within genes involved in visceral left-right
349 patterning contribute to hand preference. We consider the most likely explanation for the

discrepancy to be that the previous findings were noise, which arose from limited sample sizes. 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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493 23andMe co-president AW has provided general guidance, including guidance related to the
494 company's research undertakings and direction. PLoS Genetics' Editor-in-Chief Gregory S. Barsh is a
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583 # Supplemental Information docx

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

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

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588 # Supplemental table excel

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

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