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].

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

It has become increasingly clear during the last decade that psychiatric, cognitive and behavioural

traits are usually influenced by many genetic factors with very small effects of each individual locus,

so that tens of thousands of subjects are needed to detect effects reliably [45]. None of the studies

listed above approached that level of sample size or statistical power. Low power reduces the

likelihood that a statistically significant result reflects a true effect [46]. Most of the studies

summarized above made secondary use of datasets which were collected for different purposes, so

that left-handedness was present at only roughly 10% within the datasets. This meant that statistical

power was even less than might have been achieved in such sample sizes, for example through

selection schemes balanced for handedness. Given the statistical issues affecting the earlier studies,

it seems likely, from a contemporary perspective on statistical genetics, that most or all of the

findings were false positives.

Some of the genetic associations summarized above were identified in groups with specific disorders,

including children with reading disability [29, 42], and families with bipolar disorder [36]. Therefore,

even if the genetic associations were real, they may not extrapolate to the general population.

Finally, a variety of different measures related to handedness were used in these studies, including

binary traits based on simple questions such as 'which hand do you write with', to quantitative

indices based on the peg board test.

An opportunity arose recently to perform a high-powered GWAS of hand preference in a very large,

adult population sample from the UK, known as the UK Biobank dataset [47]. A recent study

performed separate GWAS for hundreds of different biological variables within this dataset, of which

hand preference was just one variable, being available for more than 300,000 subjects (measured by

questionnaire and analysed as a set of binary traits, see below). The genome-wide statistical

association results from all of the different GWAS were placed on the internet

(http://www.nealelab.is/uk-biobank/). Most of the GWAS, including that for hand preference, were

not further queried, interpreted or discussed. Two individual loci were significantly associated with

hand preference after adjustment for multiple testing over the genome. One locus was within a very

large region of linkage disequilibrium which arises from an inversion event on chromosome 17q21

and spans many genes, while the other was close to the gene *MAP2* (Microtubule Associated Protein

2) on chromosome 2q34. However, there may be other loci which are truly associated with hand

preference in the UK Biobank GWAS results, but which do not reach the threshold of significance to

survive correction for multiple testing over the whole genome (i.e. roughly $P=5\times10^{-8}$). SNP-based

heritability analysis, based on variation over all of the autosomes (i.e. all chromosomes minus the sex

chromosomes) arrived at explained variance (SNP-heritability) for left-handedness of only 1.8% in the

UK Biobank (p=6.4e-03), which is markedly lower than previous indications from twin studies (see

above), while ambidexterity had an estimated SNP-heritability of 6.8% (p=8.7e-04)[48].

Here, we have used the genome-wide GWAS results for hand preference in the UK Biobank to

investigate whether any of the previously reported loci, summarized above, show evidence for

association with binary trait handedness in the general adult population, as assessed in this large

dataset and well powered analysis (http://www.nealelab.is/uk-biobank/). We also applied different

methods of gene-set enrichment analysis to the GWAS results, in order to test the relevance of gene-

sets that are involved in laterality of the visceral organs.

Methods

Data

We used the data collected in the UK Biobank [47] and analysed by the Neale lab, which were

available from www.nealelab.is/uk-biobank/ [49]. Signed informed consent was obtained from all

participants, and the UK Biobank has ethical approval from the UK Biobank Research Ethics

Committee under number 16/NW/0274. Data for handedness were collected by a questionnaire with

the question "Are you right or left handed?", and as possible answers "Left-handed", "Right-

handed", "Use both right and left hands equally" and "Prefer not to say"

(http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1707). The traits investigated in the first release

from the Neale lab (September 2017) were left-handed vs 'other' (32,442 left-handed vs 304,688 not

left-handed), and ambidextrous vs 'other' (5,517 ambidextrous vs 331,613 not ambidextrous).

'Other' does not include the handful of people who ticked 'prefer not to say'. Heritability estimates

as reported above were based on this release. Samples were genetically independent and of white

British ancestry [48]. GWAS results were also available from a second release (August 2018,

http://www.nealelab.is/uk-biobank/) on 361,194 subjects. This second release included more

individuals, updated genotype data, and the addition of the X-chromosome, as well as additional

covariates for the association analysis, among which were age and age^2. The analysed traits now also

included 'right-handed vs other' (40,671 right-handers vs 320,242 non-right-handers, i.e.

ambidextrous individuals were now combined with the left-handers). This is the trait (1707.1) that

we predominantly used in the present study for our analyses (below), but we also include look-ups of

previously reported candidate SNPs in relation to the 'left-handed versus other' (34,585 cases) and

'ambidextrous versus other' (6,086 cases) results. The GWAS for ambidexterity was necessarily based

on a smaller sample size in the 'case' group than the other trait definitions, and accordingly the

power would have been lower.

The GWAS data summary file provided by the Neale lab included a column

"low_confidence_variant". We filtered out the SNPs marked 'true' in this column before further

analysis. These were often SNPs with very low minor allele frequency (MAF).

Previously implicated SNPs and genes

We checked the GWAS catalog (http://www.ebi.ac.uk/gwas/search, 3 July 2018) for the terms

'handedness' and 'hand' to find SNPs and genes previously implicated in traits related to hand

preference. In addition we checked the literature through Pubmed (July 2018) for (('hand preference'

OR 'hand skill' OR 'handedness') AND genetic) to identify SNPs or genes found in non-GWAS studies

(such as candidate gene studies). We also checked references in the papers we found. The results of

this search are summarized in the Introduction.

In the results of the UK Biobank GWAS for hand preference, we first checked the p-values for

association, for each of the specific SNPs reported in the previous papers (Table 1). We also

generated association scores for each individual gene implicated in the previous papers, by use of the

Magma program as implemented in the FUMA package v1.3.3 (see Supp. Table 1 for specific settings)

[50](August 2018). Each gene-based score summarizes the overall level of association at all SNPs

spanning a given gene, into one single score and generates a corresponding P value for that entire

gene.

Gene-sets involved in visceral laterality

To test for the involvement of genes associated with visceral asymmetry in relative hand skill,

Brandler et al. had selected a number of mouse phenotypes related to visceral asymmetry (see

Introduction), such as 'dextrocardia' and 'situs inversus', from all those available in the Mouse

Genome Informatics (MGI) resource (http://www.informatics.jax.org/). In this database, mutations in

specific genes have been linked to resulting phenotypes, such that each phenotype has a set of

individual genes annotated to it. The exact criteria by which Brandler et al. selected their specific

phenotypes for analysis were not described. In addition, new relevant mouse laterality phenotypes,

and their associated genes, may have been added since 2013. We therefore made an up-to-date

selection of phenotypes related to visceral asymmetry in the MGI, in the following way: In the

hierarchical tree for mammalian phenotypes (http://www.informatics.jax.org/vocab/mp_ontology,

MGI 6.12, last updated 06/19/2018), we searched for 'heterotaxy', 'situs inversus', 'isomerism' and

'dextrocardia', and also included all child terms if they also related to asymmetry phenotypes. We

only included terms with at least 15 genes. This approach resulted in a list of 11 mouse phenotypes

(See Results). The mouse genes were then mapped to corresponding human genes, using

homologene.data (v68, May 2014) from ftp://ftp.ncbi.nih.gov/pub/HomoloGene/current, by

matching mouse genes with human genes that had the same HID (HomoloGene group identifier). The

list of phenotypes and the associated human genes can be found in Supplementary Table 2.

In the Online Mendelian Inheritance in Man database OMIM (https://omim.org/, last updated on 26

Jun 2018), we also identified all genes in the human phenotypic series 'Primary Ciliary Dyskinesia'

(MIM # 244400), because half of the patients with this disorder present with situs inversus. These

genes were used to form one additional gene-set, thus in this study we tested a total of twelve sets,

eleven from the mouse database and one based directly on human genetics (See Results).

Seven of our mouse phenotypes were among those previously analysed by Brandler et al. (Supp.

Table 3). We also repeated our analyses using the exact same list of mouse phenotypes used by

Brandler et al. (Supp. Table 3). However, the gene lists associated with each mouse phenotype may

have changed since Brandler et al. performed their study five years ago, as new information on genes

affecting visceral asymmetry can have been incorporated.

Gene-set enrichment analysis

We ran three different gene-set enrichment algorithms that have been developed for application to

GWAS results. Brandler et al., in their investigation of gene sets involved in visceral laterality, had

used MAGENTA [51]. For consistency we also used MAGENTA (v2, 21 July 2011), plus two newer

algorithms called Magma ([52], v1.06) and Pascal ([53](no version number). The three enrichment

algorithms work in different ways, but essentially they first assign a single association score to each

genes based on the GWAS data, and then test whether the genes in a given set show, on average,

more evidence for association with the trait in question than the rest of the genes in the genome for

which scores could be calculated (hence these are sometimes called 'competitive' analyses [54]),

while accounting for non-independence of SNPs due to linkage disequilibrium. For Magma and

Pascal, we used default settings, while for MAGENTA we chose the settings as used by Brandler *et al.*

(parameter settings for all analyses can be found in Supp. Table 1). Pascal and Magma offered the

option to calculate gene-scores based on the single most associated SNP within a gene (the 'max'

option), or on a combination of SNPs within the gene (the 'sum' option), and we ran both approaches

with both softwares, for an exhaustive assessment of whether the previously implicated gene sets in

the literature might affect handedness in the UK Biobank.

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	PAS CAL SUM P	PAS CAL MAX P	MA GM A SUM P	MA GM A MAX P	MA GEN TA 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

274 *Gene set enrichment results for visceral asymmetry-related gene-sets, based on the UK Biobank*
275 *GWAS for non-right-handedness versus right-handedness, and using different softwares and settings.*
276 *See Supplementary Table 1 for the settings. The uncorrected P values for each gene set and*
277 *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

used various different trait measures related to handedness, and some made use of selected

disorder populations, then it remains possible that some of the earlier findings were indeed real, but

not detectable in the present analysis (see Introduction).

There was no evidence for an involvement, in hand preference, of common variants in genes related

to visceral left-right patterning. Note that Brandler et al. [43] performed analysis of a quantitative

handedness index based on peg moving, and included a sample with reading disability, when they

originally reported such a relationship. Our present analysis was not an attempt to directly replicate

the study of Brandler *et al.*, but rather it was a related investigation, of genes involved in visceral

asymmetry with respect to questionnaire-defined, binary-trait hand preference, in a large dataset

from the general population. In the rare genetic disorder Primary Ciliary Dyskinesia (PCD)(MIM #

244400), recessive mutations in specific genes involved in ciliary biology result in a 50% chance of

mirror-reversed left-right visceral asymmetry, a condition known as *situs inversus totalis (*SIT) [56].

When PCD and SIT co-occur (the combination is known as Kartagener syndrome), it appears that the

rate of left-handedness is unchanged from the general population [57]. However, there may be an

increase of left-handedness in people with SIT when they do not have PCD [58, 59], which would

suggest the existence of some developmental mechanisms which link visceral asymmetry with brain

asymmetry. Nonetheless, a recent genome-wide mutation screening study did not identify any

individual genes as likely candidates to cause non-PCD SIT when accompanied by left-handedness

[60], and it is possible that the aetiology is multifactorial or even non-genetic [60, 61]. At present, the

study by Brandler et al. remains the only one to report tentative evidence for a molecular genetic link

between visceral laterality and handedness.

As already noted, only two loci were found associated with non-right-handedness in the UK Biobank

GWAS. The most likely causative gene within the large chromosome 17q21 inversion cannot be

determined on the basis of these data, as the region spans at least twelve genes showing similar

levels of association with the trait. This region shows association with various other human traits (see

e.g. http://big.stats.ox.ac.uk/variant/17-44515243-C-T). For the locus on chromosome 2q34, the

most probable gene appears to be *MAP2*: the association signal extends from upstream into this

gene's coding region, and the single most associated SNP is associated with expression differences of

MAP2 in oesophageal tissue, according to the GTeX database (https://www.gtexportal.org/home/

Release V7 (dbGaP Accession phs000424.v7.p2)), and not with any other gene's expression level.

MAP2 protein is a well-known marker for neuronal cells, and specifically the perikarya and dendrites

of these cells [62]. MAP2 is involved in neurogenesis [63], and almost exclusively expressed in the

brain [64]. The protein plays a role during the development of various brain structures (e.g. [65, 66]),

and in mice seems to play a role in motor skills [67]. One report suggested that *MAP2* is more highly

expressed in right hippocampus than left during development in the rat [68]. How exactly this gene

may act in affecting motor laterality in human development remains unknown. Regardless, as the

genetic association is based on hundreds of thousands of study participants, *MAP2* must be

considered the single most reliably implicated gene in human hand preference yet identified.

However, replication is desired.

There may have been some particular sources of noise in the UK Biobank definitions of hand

preference. An earlier analysis of the UK biobank dataset [26] suggested a reduction in left-hand

preference of roughly 20% among the oldest participants (born around 1940), relative to younger

participants (born around 1970), which suggests that some of the older left-handed people were

forced to switch to right-handedness during childhood. The GWAS analysis did, however, adjust for

age as a covariate effect. In addition, the location of birth within the UK was found to influence the

probability of being left-handed [26], likely primarily for cultural rather than biological reasons. The

ambidextrous group was also found to give a high rate of inconsistent answers between different

assessment visits [26].

It is striking that common genetic variants in the UK Biobank dataset have little overall effect on hand

preference, as measured by a very low SNP-based heritability (only 2-3%)[48, 69], while previous

twin-based studies have indicated a heritability of roughly 25% for left-hand preference (see

Introduction). It has been noted before that behavioural traits can show a particularly large

difference between twin and SNP-based heritability estimates [70]. A commonly given explanation is

that much of the heritability may be due to rare SNPs and mutations, which are not well captured by

genotyping arrays and imputation protocols in GWAS studies. Rare mutations can be relatively recent

in origin, and under negative selection. Whether these possibilities apply to hand preference will

need to be investigated in future large-scale genome sequencing studies.

Conclusion

In conclusion, previously reported genetic associations with measures related to handedness, found

in datasets other than the UK biobank, were not supported by analysis of this very large cohort. We

also found no supportive evidence that common variants within genes involved in visceral left-right

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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20585627; PubMed Central PMCID: PMCPMC2891811 and own stock options in the company.

23andMe co-president AW has provided general guidance, including guidance related to the

company's research undertakings and direction. PLoS Genetics' Editor-in-Chief Gregory S. Barsh is a

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Supplemental Information docx

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

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

Supplemental table excel

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