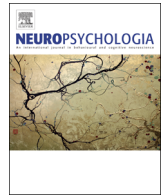




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Whole exome sequencing for handedness in a large and highly consanguineous family



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ABSTRACT

Pinpointing genes involved in non-right-handedness has the potential to clarify developmental contributions to human brain lateralization. Major-gene models have been considered for human handedness which allow for phenocopy and reduced penetrance, i.e. an imperfect correspondence between genotype and phenotype. However, a recent genome-wide association scan did not detect any common polymorphisms with substantial genetic effects. Previous linkage studies in families have also not yielded significant findings. Genetic heterogeneity and/or polygenicity are therefore indicated, but it remains possible that relatively rare, or even unique, major-genetic effects may be detectable in certain extended families with many non-right-handed members. Here we applied whole exome sequencing to 17 members from a single, large consanguineous family from Pakistan. Multipoint linkage analysis across all autosomes did not yield clear candidate genomic regions for involvement in the trait and single-point analysis of exomic variation did not yield clear candidate mutations/genes. Any genetic contribution to handedness in this unusual family is therefore likely to have a complex etiology, as at the population level.

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1. Introduction

Hand preference in humans is strongly biased to the right at the population level, and is the most overt human behavioural lateralization, with only approximately 1 in every 10 people being left-handed (Hardy and Petrinovich, 1977). Hand preference is commonly assessed by item-based questionnaires such as the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971), which produces a spectrum of hand preference in the population that has a bimodal distribution. Roughly 1% of adults show intermediate levels of hand preference defined as ambidextrous, while the great majority show a preference for one hand over the other when considered across multiple tasks (Ocklenburg et al., 2014a).

Behavioural lateralization is visible at early stages of human development. A majority of foetuses at gestational week 10 have been observed by ultrasound scanning to move their right arms more than their left (Hepper et al., 1998), in a proportion strikingly similar to adult rates of handedness. A longitudinal study also

found that foetal 'thumb sucking' at gestational age 15 was predictive of handedness at 10–12 years (Hepper et al., 2005). These behavioural lateralizations *in utero* occur before brain anatomical lateralization becomes apparent in language-related regions around the Sylvian fissure during the second trimester of gestation, and strongly indicate a genetic-developmental program for human brain and behaviour that is inherently lateralized from embryo onwards (Francks, 2015; Willems et al., 2014).

Indeed handedness is subtly related to functional language lateralization, hinting at overlapping genetic-developmental origins for these traits. While roughly 85% of humans have left-lateralized language dominance, a higher percentage of left-handers than right-handers have been observed with atypical (reduced or reversed) language lateralization, as assessed by functional transcranial Doppler sonography (fTCD) (Knecht et al., 2000) or functional magnetic resonance imaging (fMRI) (Mazoyer et al., 2014). A recent study, again using fTCD, found that the correlation between left-handedness and atypical functional language lateralization in extended families was $r=0.28$ (Somers et al., 2015). Another recent study, this time based on functional Magnetic Resonance Imaging (fMRI), found that fully reversed (i.e. rightward) functional lateralization for language was found in roughly 7% of left-handers, but not at all in right-handers (Mazoyer et al., 2014).

Brain and behavioural asymmetries are widespread across many vertebrate clades, and several species of mammals have

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shown evidence for population-level handedness or pawedness. Subtle population-level paw preference in reaching tests has been observed in inbred mice (Waters and Denenberg, 1994), although the subtlety of these lateralizations required large samples to detect them, and they varied in leftward versus rightward direction depending on the specific task (Waters and Denenberg, 1994). Rats have shown a stronger population-level bias (73% right paw preference) than mice (Guven et al., 2003). Apes have also shown evidence for population-level handedness, and some structural brain lateralizations similar to those found in regions important for language in humans (Cantalupo et al., 2009; Hopkins, 2013; Hopkins et al., 2011; Lyn et al., 2011; Meguerditchian et al., 2013). Target animacy may play a role in these preferences (Forrester et al., 2011, 2012). These various mammalian species may prove to be useful models for understanding aspects of the genetics and development of human brain lateralization, although they have been barely, or not at all, studied in this regard (Francks, 2015). The right hand is also argued to have been dominant in Neanderthals, through interpreting patterns of scratches on the incisor and canine teeth of fossils (Frayner et al., 2012).

A meta-analysis study of thousands of Australian and Dutch twin families found the heritability of handedness to be close to 25% (Medland et al., 2009a), which was measured with high-accuracy and strong statistical significance due to the large sample size involved. Single-gene models for handedness have been proposed and extensively discussed in the literature, including the 'right-shift' hypothesis of Annett (2003) (Annett and Alexander, 1996), the 'dextral/chance' hypothesis of McManus (1985), and a model proposed by Klar (1996) which assumes a recessive mode of genetic inheritance. These models integrate the concept of fluctuating asymmetry, in which loss-of-function genotypes at a hypothetical genomic locus result in randomization of lateralized brain development on the left–right axis affecting handedness. It is notable that mutations of certain genes involved in ciliary function are known to cause randomization in the direction of visceral lateralization (Hamada et al., 2002; Levin, 2005), with half of patients manifesting *situs inversus* of visceral organs and half the normal pattern.

However, a genome-wide association study (GWAS) based on 3940 twins resulted in no individual locus significantly associated to handedness after correction for multiple testing across the genome (Armour et al., 2014). This GWAS study was adequately powered to detect a major-genetic effect on handedness, if it was due to common variation in the genome. Therefore the authors estimated that at least 40 different genetic variants would be required to explain the heritable component of handedness in the population, in other words that locus and/or allelic heterogeneity was likely to be involved (Armour et al., 2014; McManus et al., 2013). A preliminary report of a GWAS from the ENGAGE Handedness Consortium, based on 23,443 subjects, also did not indicate significant evidence for association (Medland et al., 2009b).

A recently conducted linkage analyses on 37 Dutch families also did not identify genomic regions linked significantly to handedness, which was performed under the model of inheritance proposed by McManus, i.e. involving an additive genetic contribution and fluctuating asymmetry (Somers et al., 2015). This study used heterogeneity linkage analysis, which allows for possible differences in genetic effects in the separate families. An earlier linkage study based on 25 nuclear families, performed under Klar's recessive model, also found no significant results (Van Agtmael et al., 2003). A linkage study based on relative hand skill (i.e. lateralized motor performance) found suggestive loci of interest, but again no evidence for there being only one major-genetic effect on handedness in the population (Francks et al., 2002). A genome-wide linkage analysis of extended Mexican–American families also did not identify genomic regions significantly linked to handedness,

and the suggestively linked regions were noted to be devoid of obvious candidate genes (Warren et al., 2006).

The combined, very small effects of many thousands of polymorphisms may also affect handedness, together with unknown environmental factors (one known factor is the phenomenon, more prevalent historically, of encouraging or forcing left-handers as children to do things with their right hands (Grabowska et al., 2012; Kloppel et al., 2010)). Initial findings of small individual genetic effects involve the genes Leucine-Rich Repeat Transmembrane neuronal 1 (*LRRTM1*) and Proprotein Convertase Subtilisin/Kexin Type 6 (*PCSK6*), which were both found in a set of families in which at least one sibling had dyslexia, and using measures of lateralized manual performance based on peg moving (Arning et al., 2013; Francks et al., 2007; Scerri et al., 2011). *LRRTM1* is a transmembrane protein involved in the differentiation of excitatory synapses (Linhoff et al., 2009). It is not known if *LRRTM1* contributes to the development of brain lateralization. *PCSK6* is a protease that cleaves NODAL, a member of the transforming growth factor beta (TGF β) superfamily involved in visceral organ lateralization, but again with no functional evidence for a role in brain lateralization. The *PCSK6* gene has also been proposed to affect the degree rather than the direction of lateralized hand performance (Arning et al., 2013). In general it is not clear that visceral and brain lateralization are closely linked developmentally, because people with *situs inversus* (visceral organs reversed on the left–right axis), and having the genetic condition Primary Ciliary Dyskinesia (PCD), did not show changes in rates of left-handedness or left-lateralized auditory language dominance in the largest studies of these issues to have been performed (McManus et al., 2004; Tanaka et al., 1999). Another genetic study of handedness focused on a repeat-length polymorphism at the androgen receptor locus on chromosome X, and found that the number of repeats was associated with handedness (Arning et al., 2015). However, each of these genetic findings requires further validation. Additional small genetic effects, potentially influencing aspects of brain and behavioural lateralization other than handedness, have been reviewed elsewhere (Francks, 2015; Ocklenburg et al., 2014b).

Although the above genetic linkage and association studies of handedness appear to rule out major genetic effects that are due to common variation in the genome, it remains possible that certain individual, extended families with elevated rates of non-right-handedness may have relatively rare or unique genetic sub-forms of the trait that are affected disproportionately by a single gene mutation. Although one previous study used heterogeneity linkage analysis (Somers et al., 2015), few of the individual families in that study were large enough to provide adequate statistical power to detect significant linkage, in the case of extensive heterogeneity of effects between families. In the present study we have considered a recessive major-genetic model in a single, large, extended family from Pakistan with multiple instances of consanguineous marriage and an elevated rate of non-right-handedness in the younger generations. Consanguinity is known to increase the chances of having recessive genetic traits and disorders in offspring, since offspring are likely to inherit two copies of sections of the genome identical-by-descent, and homozygous for any genetic mutations within those regions.

We performed whole exome sequencing using next generation DNA sequencing in 17 members from this family, which allowed us to perform not only a classical recessive linkage scan, but also systematic screening of DNA sequence variants affecting the protein-coding portion of genes in potentially linked regions of the genome. The exome is the roughly 1–2% of the genome that codes for proteins. In our analysis we allowed for incomplete penetrance (90%; i.e. allowing a 10% chance that a recessive mutation might not cause non-right-handedness) and 10% phenocopy (i.e.

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