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Chapter 16

Large-scale genetic mapping for human brain asymmetry

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Abstract

Left–right asymmetry is an important aspect of human brain organization for functions including language and hand motor control, which can be altered in some psychiatric traits. The last 5 years have seen rapid advances in the identification of specific genes linked to variation in asymmetry of the human brain and/or handedness. These advances have been driven by a new generation of large-scale genome-wide association studies, carried out in samples ranging from roughly 16,000 to over 1.5 million participants. The implicated genes tend to be most active in the embryonic and fetal brain, consistent with early developmental patterning of brain asymmetry. Several of the genes encode components of microtubules or other microtubule-associated proteins. Microtubules are key elements of the internal cellular skeleton (cytoskeleton). A major challenge remains to understand how these genes affect, or even induce, the brain's left–right axis. Several of the implicated genes have also been associated with psychiatric or neurologic disorders, and polygenic dispositions to autism and schizophrenia have been associated with structural brain asymmetry. Knowledge of developmental mechanisms that lead to hemispheric specialization may ultimately help to define etiologic subtypes of brain disorders.

INTRODUCTION

Population-level asymmetries of anatomy and function arise in the human brain during fetal development, and behavioral asymmetry has been reported as early as 10 weeks of gestational age (Hepper et al., 1998, 2005; Kasprian et al., 2011; Abu-Rustum et al., 2013; Duboc et al., 2015; Taymourtash et al., 2023). Prenatal asymmetries include left-lateralized functional connectivity of the temporal lobe (Taymourtash et al., 2023) and right-lateralized predominance of arm movements (Hepper, 2013). These developmental asymmetries are likely to be precursors of left-hemispheric language dominance and right-handedness. The early appearance of brain and behavioral asymmetries indicates a genetically regulated program of left–right axis formation in the central nervous system (Francks, 2015; Gunturkun and Ocklenburg, 2017; de Kovel et al., 2019; Francks, 2019; Sha et al., 2021b).

Consistent with a genetic origin, twin- and family-based analyses have reported heritability of up to roughly 30% for measures of brain structural or functional asymmetry, particularly those linked to regions or networks important for language (Guadalupe et al., 2017; Kong et al., 2018; Somers et al., 2015; Labache et al., 2023), although heritability of hemispheric language dominance has not always been found (Bishop and Bates, 2019). Left-handedness also has a heritability of roughly 25% in twin-based analysis (Medland et al., 2009) and 1%–6% in population studies that have examined the contribution of common genetic variants specifically (de Kovel and Francks, 2019; Cuellar-Partida et al., 2021).

In addition, studies have measured molecular asymmetries in small numbers of postmortem tissue samples from matched left and right brain regions of the prenatal or adult central nervous system, in terms of messenger RNA, protein, or DNA methylation (Sun et al., 2005; Karlebach and Francks, 2015; de Kovel et al., 2017, 2018; Muntané et al., 2017; Ocklenburg et al., 2017; Zhao et al., 2022b). These postmortem studies have been reviewed previously (Schmitz et al., 2019), and we will not cover them again here. They have provided snapshots of potential molecular asymmetries in the human brain at specific life stages, including the possibility of left–right differences of maturation rates during fetal development, and asymmetries of glutamate receptor expression in the adult cerebral cortex.

In this chapter, we will instead review recent studies that have associated particular genetic variants with interindividual differences in brain asymmetry or handedness. After roughly two decades during which these kinds of studies produced tentative findings in

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limited sample sizes (reviewed by Schmitz et al., 2019; de Kovel and Francks, 2019), progress was suddenly accelerated during the past 5 years by large-scale genome-wide association analyses, carried out in general population samples ranging from roughly 16,000 to over 1.5 million participants (de Kovel and Francks, 2019; Wiberg et al., 2019; Carrion-Castillo et al., 2020; Le Guen et al., 2020; Cuellar-Partida et al., 2021; Kong et al., 2021; Sha et al., 2021a,b; Zhao et al., 2022a). We will focus on the findings from this new generation of large-scale genetic association studies.

Altered brain asymmetries have been reported in various psychiatric disorders (DeLisi et al., 1997; Shenton et al., 2001; De Fosse et al., 2004; Herbert et al., 2005; Kawasaki et al., 2008; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Carper et al., 2016; Okada et al., 2016; Markou et al., 2017; Ravichandran et al., 2017; Sun et al., 2017; Grove et al., 2019; Postema et al., 2019; Floris et al., 2021; Kong et al., 2022), including by recent consortium studies that have helped to overcome some of the statistical uncertainty of earlier literature (Postema et al., 2019; Kong et al., 2020; Postema et al., 2021; Schijven et al., 2023). The consortium studies have found various aspects of brain structural asymmetry to be subtly altered in autism (Postema et al., 2019), schizophrenia (Schijven et al., 2023), obsessive-compulsive disorder (Kong et al., 2020), and attention deficit-hyperactivity disorder (Postema et al., 2021). In addition, meta-analyses have indicated that left-handedness occurs at increased rates in neurodevelopmental and psychiatric conditions, including intellectual disability (Papadatou-Pastou and Tomprou, 2015), autism (Markou et al., 2017), schizophrenia (Hirnstein and Hugdahl, 2014), and reading or language impairment (Abbondanza et al., 2023). These associations suggest that population-typical asymmetries are linked to optimal brain function and raise the possibility of shared genetic contributions to brain asymmetry and disorders. Toward the end of this chapter, we will summarize findings from recent large-scale genetic studies that have supported such a link between brain asymmetry and disorders.

GENOME-WIDE ASSOCIATION STUDIES OF BRAIN STRUCTURAL ASYMMETRY

In 2020, the first two large-scale genome-wide association studies of specific aspects of human brain structural asymmetry were published (Carrion-Castillo et al., 2020; Le Guen et al., 2020). These studies made use of the UK Biobank database (Alfaro-Almagro et al., 2018; Bycroft et al., 2018), which at that time included brain imaging and genetic data from roughly 16,000–18,000 participants, depending on study-specific details of MRI processing and quality control. The UK Biobank is a general population dataset of middle-aged to older adults, and the imaging genetics dataset has since roughly doubled in size (and further data collection and releases are on-going). It became a mainstay for many of the studies described further below, as it is unique in terms of homogeneous data collection from such a large sample size.

The study by Carrion-Castillo et al. (2020) targeted asymmetry of the *planum temporale*, a region of the superior temporal auditory and language cortex whose asymmetry has long been studied in relation to possible associations with hemispheric language dominance, reading- and language-related impairments, and other brain disorders (Sommer et al., 2001; Knaus et al., 2010; Altarelli et al., 2014; Tzourio-Mazoyer et al., 2018). *Planum temporale* volume asymmetry was found to have a significant heritability of roughly 14%, and two genomic loci were associated with its variability, one of which was a protein-altering variant within the gene ITIH5 (Carrion-Castillo et al., 2020). The functions of this gene are not well understood, but it may be involved in stabilization of the extracellular matrix (the network of proteins and other molecules that surround and support cells within tissues), and it has high expression in endothelial cells, which suggests a role in the blood–brain barrier. The mechanisms by which *ITIH5* might affect asymmetry of the superior temporal cortex are not known, especially as this gene is relatively uniformly expressed across the cortex. Interactions of the ITIH5 protein with other, as-yet-unidentified proteins that show more regional and hemisphere-specific expression patterns may underlie its association with *planum temporale* asymmetry. In principle, such processes may occur developmentally—for example, during fetal stages—and/or later in life with respect to age-related changes of asymmetry during adulthood (Roe et al., 2021). We will return to these possibilities further below.

The study by Le Guen et al. (2020) focused on the anatomy of the superior temporal asymmetric pit, a part of the superior temporal sulcus that is located beneath the primary auditory cortex of Heschl's gyrus. The superior temporal asymmetric pit may be a human-specific feature that was involved in the evolution of language. Its depth on the left hemisphere was found to associate with a locus near to the gene *DACT1,* which was also the case on the right hemisphere, but to a lesser extent than the left. This pattern resulted in an association of the *DACT1* locus with asymmetry. *DACT1* is involved in regulation of intracellular signaling pathways during development, which may include very early embryonic morphogenesis as well as later neuronal differentiation.

Unlike *ITIH5*, where a protein-altering genetic variant was associated with structural brain asymmetry, the genetic variant close to *DACT1* does not alter a protein sequence and is more likely to exert a regulatory effect on gene expression at the level of messenger RNA. This means that there is some uncertainty about whether the association of the *DACT1* locus with brain asymmetry is in fact mediated through *DACT1* itself, or through another nearby gene in the genome whose expression might also be affected by the same genetic variant. In fact, most of the genetic associations found in the studies described in this chapter are of this latter type, i.e., where there is some uncertainty about the causal gene pertaining to any given genetic association. The effect at ITIH5 is relatively unusual in this respect, as it directly implicates a specific gene through altering its protein sequence. The uncertainty at most loci can be partly mitigated through the use of gene set (or pathway) analysis, as will be seen below.

In 2021, a genome-wide association study of human structural brain asymmetry was published (Sha et al., 2021b) that had three important features that enabled more extensive discovery than previously. First, the study was based on an updated release of the UK Biobank data that yielded a sample size of over 32,000

individuals—roughly twice that of previous studies—with a consequent boost to statistical power to detect genetic effects. Second, the study considered structural asymmetries of gray matter thickness and surface area for regions spanning the entire cerebral cortex, as well as volumetric asymmetries of subcortical structures (including the thalamus, hippocampus, and striatal structures), rather than focusing on just one region of the brain. Third, the study used multivariate genetic association mapping, where each variant in the genome was tested for its simultaneous association with all heritable regional asymmetry measures. This approach explicitly modeled how each genetic locus can affect asymmetry to a greater or lesser extent across multiple brain regions, which again likely enhanced the statistical power to detect genetic effects.

Sha et al. (2021b) calculated hemispheric asymmetry indexes as (left–right)/((left+right)/2) for each pair of corresponding left-to-right structural measures in the UK Biobank data and found that 42 regional asymmetries showed significant heritability based on common single nucleotide variants in the genome (i.e., with population frequencies above 1%). The heritability ranged from only 2.2% for the asymmetry of entorhinal cortical thickness to 9.4% for the asymmetry of the superior temporal surface area. The overall pattern across regional asymmetry measures was consistent with previous twin-based heritability analyses (Guadalupe et al., 2017; Kong et al., 2018), although twin-based heritability had been reported as somewhat higher, up to roughly 25% for certain brain regional asymmetries. Twin-based heritability is often measured to be higher than that based on common single nucleotide variants alone, which is unsurprising because common single nucleotide variants are just one class of genetic variation (others include rarer mutations and larger genomic structural variants). In addition, twin studies can overestimate heritability when certain assumptions are not fully met (Young, 2019).

In multivariate genome-wide association testing, Sha et al. (2021b) found 27 independent genetic variants that were significantly associated with different aspects of structural brain asymmetry (Fig. 16.1). Strikingly, almost half of these genetic loci implicate genes that either code for components of microtubules called *tubulins*, or else other proteins that directly interact with, or modify, microtubules. Microtubules are prominent parts of the cytoskeleton—the framework of protein filaments internal to cells—that contribute to a wide range of processes including cellular growth, division, migration, shape and axis formation, axon outgrowth and intracellular transport (Janke and Magiera, 2020).

Gene-set enrichment analysis confirmed that genetic variants associated with structural brain asymmetry tend to be located in the genome close to, or within, microtubule-related genes more often than expected by chance. Therefore, even though the causal gene might be uncertain at any single locus (see above), the overall tendency for the loci to be within or near microtubule-related genes means that the causal gene at any given locus is likely to be the nearest microtubule-related gene. Specific microtubule-related genes implicated in structural brain asymmetry by Sha et al. (2021b) code for the tubulins TUBB, TUBB3, TUBB4A, and TUBA1A/TUBA1B/TUBA1C (the genes for these latter three proteins are clustered together on chromosome 12), as well as microtubule-associated proteins MAPRE3, AGBL5, MAP2, DAAM1, and MAPT.

Other loci associated with structural brain asymmetry by Sha et al. (2021b), but which did not directly implicate microtubule components or associated proteins, included the DACT1 and ITIH5 loci that were previously reported (see above), as well as nine others known to affect brain phenotypes or development. The DACT1 locus was now shown to associate with not only asymmetry of the language-related superior temporal sulcus and transverse temporal (Heschl's) gyrus, but also asymmetry of the pericalcarine cortex, which is located medially in the occipital lobe and best known for its functions in the visual system. In fact, almost all of the loci identified by Sha et al. (2021b) were associated with asymmetries of more than one brain region, and the regions were often spatially separated for any given genetic locus (Fig. 16.1). This suggests that the asymmetries of spatially distinct regions might share common ontological mechanisms, and/or that some mechanisms which underlie adult age-related changes of asymmetry are shared across distinct brain regions.

Given the increased sample size of Sha et al. (2021b) compared to previous studies, as well as the multivariate approach of Sha et al. (2021b), the ITIH5 locus was even more significantly associated with brain structural asymmetry than before, with a point-wise P value of 4.75×10^{-38}. Note that such a low P value does not indicate a large effect—rather, it reflects a robust, small-effect association in a sample size of over 32,000 individuals. Other genes implicated by Sha et al. (2021b) in structural brain asymmetry included *ZIC4,* which is involved in visual and auditory pathway development, *NR2F1* involved in neural activity during cortical patterning, *BBS9* which causes retinopathy and intellectual disability when mutated, *FLRT3* which regulates axon guidance and excitatory synapse development, and *COL18A1* involved in neural tube closure during embryonic development.

When analyzing their results jointly with postmortem mRNA expression data from human brain samples across the lifespan, Sha et al. (2021b) discovered that genes associated with interindividual variation in structural brain asymmetry in adults tend to be most strongly expressed during early and mid-prenatal stages. This suggests that at least some of the heritable variation in adult structural brain asymmetry is established early in life, and therefore that it remains partly stable throughout life. Indeed, some of the implicated genes—including the microtubule-related genes—may be involved in developmental mechanisms that create the left–right axis in the central nervous system, possibly within the first month after conception. Others of the implicated genes may then help to implement a downstream program of asymmetric brain development and/or lifespan change, after the initial establishment of the left–right axis. We will return to these possibilities further below.

In addition to the above studies that focused on the genetics of regional measures of structural brain asymmetry (in univariate or multivariate analytic contexts), two recent studies have focused on the genetics of global "torque" of the human brain (Kong et al., 2021; Zhao et al., 2022a). Torque refers to a population-level tendency for the right cerebral hemisphere to be situated slightly

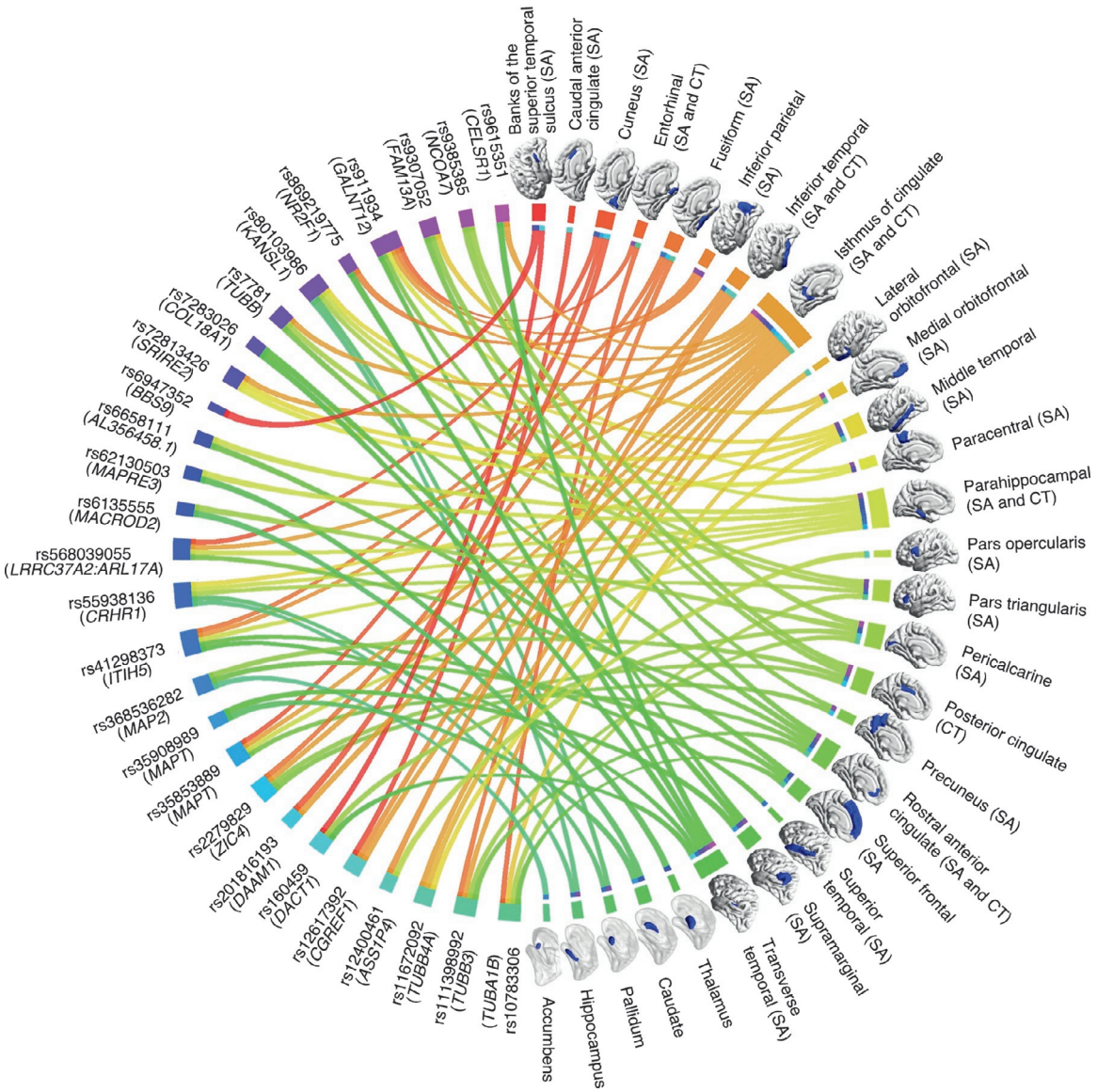

Fig. 16.1. Overview of genetic variants identified by genome-wide scanning for human structural brain asymmetry in 32,256 adult individuals. The genetic variants are indicated on the left of the circle, and they are connected by lines to the specific regional asymmetries with which they showed multivariate associations. Different colors indicate different variants or regional asymmetries. Lines linking variants to regional asymmetries are colored according to the regions. The nearest gene to each variant is shown. SA, surface area; CT, cortical thickness; SUB, subcortical volume. Figure reproduced from Sha Z, Schijven D, Carrion-Castillo A, et al. (2021b). The genetic architecture of structural left–right asymmetry of the human brain. Nat Hum Behav 5: 1226–1239.

anteriorly to the left, sometimes with the anterior right and occipital left hemispheres crossing over the midline. This pattern results in a counterclockwise skew when visualized from above (Toga and Thompson, 2003).

Kong et al. (2021) worked with the UK Biobank data to measure brain skew in the horizontal plane, using an approach based on registration to an artificially symmetrized atlas. They also confirmed a related skew in the vertical plane, whereby the right hemisphere is positioned slightly dorsally relative to the left in the majority of people. Both horizontal and vertical skews showed considerable but largely uncorrelated interindividual variation, and each was independently associated with handedness (the average skew in left-handers was reduced in the horizontal plane, but increased in the vertical plane). These average patterns and associations were also confirmed by Kong et al. (2021) in other smaller datasets. However, although the two skew measures showed SNP-based heritabilities of 4%–13%, they also showed substantial polygenicity in causal mixture model analysis, and no individually significant loci were found in genome-wide association analysis based on nearly 34,000 individuals from the UK Biobank. An even larger sample will probably be needed to reveal individually significant loci for brain torque as measured in this way.

Zhao et al. (2022a) worked with an earlier (smaller) release of the UK Biobank data, in combination with other datasets, for a total

of over 24,000 individuals. They applied three-dimensional brain shape analysis to measure multiple aspects of torque, which included frontal and occipital protrusion and midline crossing, bending, dorsoventral shift, tissue distribution asymmetries, and cerebral cortical surface positional asymmetries. All together, this resulted in hundreds of different structural brain measures, some of which showed associations with age, sex, handedness or verbal-numerical reasoning. Zhao et al. (2022a) then carried out univariate genome-wide association scanning for each of these measures separately, which produced numerous individual loci at a lenient threshold for multiple testing correction (i.e., when correcting for multiple testing across the genome but not for the number of brain measures). Only two loci were significant after strict multiple testing correction, which were not in the immediate vicinity of protein-coding genes. Again, an even larger sample will be needed to firmly implicate specific loci in brain torque.

GENOME-WIDE ASSOCIATION STUDIES OF HANDEDNESS

Roughly 90% of the population is right-handed and 10% left-handed, and this bias has been broadly consistent across cultures, ethnicities, and human history, with a limited degree of geographic and temporal variation (Coren and Porac, 1977; Perelle and Ehrman, 1994; Faurie and Raymond, 2004; McManus, 2009; Papadatou-Pastou et al., 2020). Handedness is a prominent behavioral manifestation of brain asymmetry, because right-handedness reflects left-hemisphere dominance for hand preference, and vice versa (Willems et al., 2014). As handedness is relatively easily measured by questionnaire, the sample sizes available for genetic studies have been much larger than MRI-based studies of brain asymmetry.

In 2019, the first two large-scale genome-wide association studies of human handedness were published (de Kovel and Francks, 2019; Wiberg et al., 2019), both based on the UK Biobank data, which permitted sample sizes of over 30,000 left-handers and 300,000 right-handers. As both studies were based on the same dataset, they both obtained similar results, although the findings varied slightly due to differences in quality control parameters, methodological choices, confound variables to include, and so on. These studies identified three or four loci that surpassed the threshold for statistical significance in the context of genome-wide multiple testing. The implicated genes included *TUBB*, which encodes a tubulin subunit, and *MAP2* and *MAPT*, which encode microtubule-associated proteins. The exact number of loci depended on the inclusion or exclusion of around 5000 individuals who reported using both hands equally. [This "ambidextrous" phenotype was found to be unstable in individuals who reported their handedness on multiple visits to a UK Biobank assessment center (de Kovel et al., 2019)].

Then, in 2021, a genome-wide association meta-analysis study was published based on data from the UK Biobank in addition to many other datasets from around the world, for a total of 194,198 left-handed and 1,534,836 right-handed participants (Cuellar-Partida et al., 2021). The greater statistical power of this larger study resulted in 41 genomic loci being associated with left-handedness, including at least eight that implicated microtubule-related genes and others involved in axon development and neurogenesis. A separate analysis of 37,637 ambidextrous vs 1,422,823 right-handed individuals produced 7 genomic loci, with some overlap with those from the left-handed vs right-handed analysis.

Like de Kovel and Francks (2019), the larger study by Cuellar-Partida et al. (2021) found no support for genes that were implicated by very much smaller studies over the preceding decades. This has been a feature of human genetics research in general, i.e., that large-scale genome-wide association studies have often not supported earlier findings from smaller samples. For some common diseases, the paradigm shift in scope and scale of genetic studies began already around 2007 (Burton et al., 2007), whereas for handedness and brain asymmetry the period 2019–2021 was the turning point. Genome-wide association studies in large samples have at least two crucial benefits for finding robust results. First, a large sample size improves statistical power, which is important for detecting effects and also increases the likelihood that statistically significant effects are true (Button et al., 2013). Second, a genome-wide approach is unconstrained by prior hypotheses about trait etiology. This is advantageous when studying complex, multifactorial traits like handedness or brain asymmetry, for which no single mechanism is likely to underlie the heritable variance.

GENE-BRAIN-HANDEDNESS ASSOCIATIONS

The findings summarized above refer to gene-brain or gene-handedness associations. It is also of interest to identify three-way associations—between genetic variants, brain structural/functional measures, and handedness as a behavioral variable. Such gene-brain-behavior associations can be especially informative about molecular and neurobiologic mechanisms underlying lateralized behavior.

In the UK Biobank data, Wiberg et al. (2019) examined temporal correlation data derived from resting-state functional MRI and found that left-handedness was associated with (i) decreased functional connectivity between core regions of the left-hemisphere language network, (ii) increased functional connectivity between the homologous regions of the right hemisphere, (iii) increased functional connectivity between the left and right counterparts. A similar pattern has also been reported in independent data (Labache et al., 2020). Wiberg et al. (2019) then found that a genetic variant associated with left-handedness in their genome-wide scan—rs199512—was also associated with white matter structural connectivity in tracts linking core regions of the language network. In addition, this genetic variant is associated with the expression level of the gene that encodes microtubule-associated protein MAPT, although the variant may also influence the expression of other genes, and is located within the genomic locus of *WNT3*. In fact, this locus on chromosome 17q21 is unusual in having especially long-range linkage disequilibrium (nonindependent co-occurrence of alleles at different polymorphic sites), which relates partly to a common inversion polymorphism that spans almost one million DNA bases

and several genes (Alves et al., 2015). The *MAPT* locus is particularly complex in terms of pinpointing the causal gene, or genes, that might mediate the effects of genetic variants on brain and behavioral traits. This locus is also associated with a multitude of different structural and functional brain traits, not limited to asymmetry or language regions/connections (Smith et al., 2021). We will revisit the *MAPT* locus later when discussing genetic links between brain asymmetry and brain disorders.

The largest genome-wide study of structural brain asymmetry (Sha et al., 2021b) and that of handedness (Cuellar-Partida et al., 2021) identified several genetic loci in common, which included the *MAPT* locus and several other microtubule-related genes: *MAP2*, *TUBA1A/TUBA1B/TUBA1C*, *TUBB*, *TUBB3*, and *TUBB4A*. These concordant findings firmly established microtubule biology in the heritability of both brain asymmetry and behavioral asymmetry. They also motivated a subsequent study in the UK Biobank that integrated all three levels of analysis: genomic variation, brain structural asymmetry, and handedness (Sha et al., 2021a), which we will now discuss in some detail.

Despite decades of previous research, the cerebral cortical structural correlates of handedness have remained uncertain, likely due to varying methods and limited sample sizes (as summarized by Sha et al., 2021a). Even a relatively large study of 608 left-handers vs 7243 right-handers did not find clear evidence for altered cerebral cortical anatomy in left-handedness (Kong et al., 2018). The latter study screened the cerebral cortex using atlas-defined regions (34 regions per hemisphere), but the possibility remained that structural correlates of handedness were too focal to be captured by the relatively large parcellations defined in that brain atlas.

Therefore, Sha et al. (2021a) mapped cerebral cortical structural asymmetry with respect to handedness using a higher-resolution, atlas-free approach in 3062 left-handers and 28,802 right-handers from the UK Biobank. They measured asymmetries of cortical surface area and thickness at each of 8681 "vertices" in each hemisphere, where vertex-wise correspondence between the left and right hemispheres was achieved through resampling each individual's cortical surface model to a symmetric template (Greve et al., 2013; Maingault et al., 2016). This approach aligned cortical folding patterns across individuals and hemispheres.

Sha et al. (2021a) found that left-handed people had very subtle but statistically significant group-average alterations of cortical surface area asymmetry, or cortical thickness asymmetry, of quite focal "clusters" located within the fusiform, anterior insula, precentral, postcentral, anterior-middle-cingulate and inferior occipital cortex (Fig. 16.2). Strikingly, for all of these clusters, the alterations were consistent with a relative shift of neural resources to the right hemisphere in left-handers, i.e., to the hemisphere that controls the preferred hand in left-handers. Functional annotation of the regions with altered *surface area* asymmetry in left-handers, based on meta-analyzed functional MRI data, pointed to their involvements in executive functions including working memory, as well as language and reading, mood and pain perception. In contrast, functional annotation of the cortical regions with altered *thickness* asymmetry in left-handers indicated hand sensorimotor functions (driven by a cluster in the primary sensorimotor cortex of the postcentral gyrus) and vision (driven by a cluster located in the occipital lobe).

Sha et al. (2021a) then showed that 18 of the 41 handedness-associated genomic loci reported by Cuellar-Partida et al. (2021)

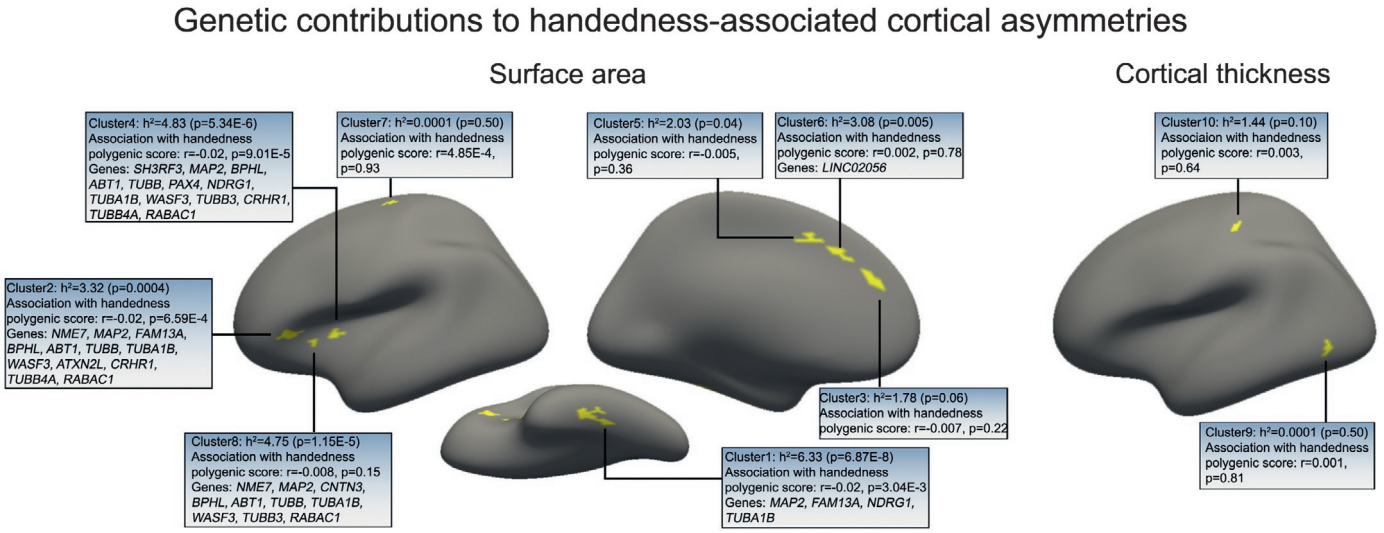

Fig. 16.2. Genetic effects on human handedness also associate with specific cerebral cortical asymmetries that are linked to handedness in 31,864 adult individuals. Ten distinct cortical clusters showed rightward shifts of surface area or thickness asymmetry in left-handers. For surface area asymmetry, five of the clusters showed significant heritability after false-discovery-rate correction (i.e., three clusters in the anterior insular cortex [clusters 2, 4, and 8], one in the fusiform cortex [cluster 1], and one in the anterior-middle-cingulate cortex [cluster 6]). Other handedness-associated asymmetry clusters were not significantly heritable, including the pre- and postcentral clusters of the sensorimotor cortex (clusters 7 and 10) and the inferior occipital cortex (cluster 9). The associations of cortical asymmetries with polygenic disposition to left-handedness are indicated, as well as individual handedness-associated genes implicated in their variabilities. Figure reproduced from Sha Z, Pepe A, Schijven D et al. (2021a). Handedness and its genetic influences are associated with structural asymmetries of the cerebral cortex in 31,864 individuals. Proc Natl Acad Sci U S A 118: e2113095118.

were also associated with at least one of the cortical surface area asymmetry clusters that are linked to left-handedness, thereby identifying a set of gene-brain-behavior associations (Fig. 16.2). The implicated genes again included several that encode components of microtubules, TUBB, TUBA1A/TUBA1B/TUBA1C, TUBB3, and TUBB4A, as well as microtubule-associated proteins MAP2, MAPT, and NME7. Interestingly, recessive mutations in *NME7* cause *situs inversus totalis*, a rare condition in which the visceral organs (heart, liver, etc.) are reversed in their orientation on the left–right axis (Reish et al., 2016). We will discuss visceral laterality further below (see also Chapter 5 in this volume). Other genes implicated by Sha et al. (2021a) to affect both handedness and its cerebral cortical correlates included *CNTN3*, which mediates cell surface interactions during nervous system development (Mohebiany et al., 2014), and *ATXN2L*, implicated in macrocephaly (Alzahrani et al., 2021).

For each of the UK Biobank participants with brain MRI and genetic data, Sha et al. (2021a) also calculated their polygenic disposition to left-handedness, based on the combined effects of variants all over their genomes. Polygenic disposition to left-handedness was associated with the handedness-linked asymmetries of surface area in the fusiform cortex and anterior insular cortex (Fig. 16.2). Specifically, higher polygenic disposition to left-handedness was associated with a relatively rightward shift of *surface area* asymmetry in these cortical regions—the same as for left-handedness itself, whereas regional cortical *thickness* asymmetries that were associated with hand preference (within the postcentral gyrus and inferior occipital cortex) were not significantly heritable and showed no associations with polygenic disposition to left-handedness (Fig. 16.2).

Causal mediation modeling (a statistical approach that seeks to explain the observed relationship between two variables via the inclusion of a third variable) was compatible with fusiform and anterior insula surface area asymmetries partly mediating the effect of polygenic disposition on hand preference. However, mediation models could also be fitted the other way around, i.e., with hand preference partly mediating an effect of polygenic disposition to left-handedness on these particular brain asymmetries. Both models can be considered possible, because the brain's structure may be both causal to behavioral outcomes and shaped plastically by repeated behavior [or correlated due to other shared underlying factors (Bishop, 2013)]. The cortical asymmetries that share genetic influences with hand preference, such as asymmetry of the language-related anterior insula surface area, suggest genetic, developmental, and perhaps evolutionary links between language and handedness. Such links have been envisaged before (Corballis, 2003). In contrast, nonheritable cortical correlates of hand preference, such as asymmetry of primary sensorimotor cortical thickness, may reflect plastic "use-based" brain responses that are relatively distal to primary mechanisms of asymmetry formation in the developing brain.

A ROLE FOR MICROTUBULES IN LEFT–RIGHT AXIS FORMATION?

In seeking the developmental mechanisms of human brain asymmetry, it is worth considering what is known of mechanisms that lead to visceral organ asymmetries in the body cavity (the heart, liver, etc.). An important mechanism involved in vertebrate visceral development involves motile cilia, which are cellular organelles that project from the cellular surface and can beat/rotate to produce an extracellular fluid flow (Norris, 2012). Life on earth is based on L-form amino acids rather than the mirror D-form, and this chirality (an object is chiral if it cannot be superposed on its mirror image) carries through to the macromolecular scale to influence the structure and movement of motile cilia (Fliegauf et al., 2007; Norris, 2012), i.e., they tend to move in one particular orientation. This results in unilateral fluid flow that can trigger asymmetric gene expression in early mammalian embryos (Norris, 2012). After asymmetry of key signaling molecules and transcription factors is established (transcription factors regulate the expression of other genes), lateralized downstream developmental programs can proceed, that are ultimately translated into asymmetries of organ morphology and positioning.

What might this mean for the brain? As reviewed above, microtubule-related and embryonically expressed genes have now been robustly associated with variation in adult human brain asymmetry and handedness by large-scale genetic studies. Microtubules are essential components of motile cilia, supporting their hairlike structure and contributing to their motility. Therefore, embryonic motile cilia might seem to provide a common mechanism for the developments of brain and visceral asymmetry. However, left-hemisphere dominances for language and hand articulation do not usually reverse in people with the rare condition of *situs inversus,* i.e., reversal of the visceral organs on the left–right axis, when caused by genetic mutations that impair motile ciliary function (Tanaka et al., 1999; McManus et al., 2004; Vingerhoets et al., 2018; Postema et al., 2020). Also, mutations in tubulin genes themselves are not known as causes of *situs inversus* of the viscera. These observations suggest at least a partial disconnect between brain and visceral organ asymmetry development and also mean that the fundamental mechanisms of brain left–right axis formation remain unknown in our species, or indeed in any mammal.

As essential components of the cytoskeleton, microtubules can also contribute to *chirality* at the whole-cell scale, i.e., create unidirectional biases in the morphology, position, rotation, or migration of cells (Tee et al., 2015), or the intracellular distributions of organelles (Fan et al., 2019). Studies in invertebrates and frog embryos have indicated that the cytoskeleton can induce asymmetric morphology of various organs through affecting cellular chirality within embryonic precursors of the organs concerned (McNiven and Porter, 1988; Steinhauer and Kalderon, 2006; Okumura et al., 2008; Lobikin et al., 2012; Tee et al., 2015; Davison et al., 2016; Inaki et al., 2016; McDowell et al., 2016). These mechanisms can be organ-intrinsic, i.e., arise independently of other developing organs or systems. Thus, the nonciliary cytoskeleton can be a source of left–right axis creation, in addition to microtubules within cilia. An organ-intrinsic, microtubule-based, but nonmotile-ciliary mechanism of brain left–right axis formation would not only fit the genetic findings pertaining to brain asymmetry and handedness but also explain the degree of apparent disconnect of brain asymmetries from visceral asymmetries (Tanaka et al., 1999; McManus et al., 2004;

Vingerhoets et al., 2018; Postema et al., 2020; Sha et al., 2021b). Such a mechanism may occur very early in development, for example, during formation of the neural tube, which in humans begins in the third week postconception (Sadler, 2005).

It is particularly relevant that Sha et al. (2021a) implicated the gene *NME7* in affecting hand preference and handedness-associated cortical surface area asymmetries. Recessive mutations in this gene cause *situs inversus* of the viscera, but ciliary functions remain intact in the affected people (Reish et al., 2016). The NME7 protein associates with γ-tubulin and the microtubules within cilia (Reish et al., 2016), which means that it can not only potentially influence cilia but also the microtubule cytoskeleton more broadly. Again, this could fit with a mechanism of brain asymmetric development that is based on cellular chirality and partly independent from ciliary-based mechanisms of visceral laterality formation. Alternatively, if motile cilia are involved in creating human brain asymmetry, then perhaps those in the embryonic nervous system have a somewhat distinct composition from those in other organs or developmental stages. Primary (non-motile) cilia may also be involved.

It is also likely that microtubule-related genes influence inter-individual variation in adult brain asymmetry in other ways, apart from a putative role in embryonic left–right axis creation. As mentioned further above, microtubules are ubiquitous components of cells throughout the lifespan and they affect a myriad of cellular properties. Mutations in some tubulin genes cause rare neurologic disorders that are likely to involve altered neuronal migration, differentiation, axon guidance, and maintenance (Tischfield et al., 2011). Mutations in *TUBB2B* can cause asymmetric polymicrogyria (many and small folds) of the cerebral cortex (Jaglin et al., 2009), while mutations in *TUBB3* can cause asymmetric cortical dysplasia and unilateral hypohidrosis (reduced sweating on one side of the body, thought to be linked to disrupted function of the cortex, brain stem, and spinal cord) (Fukumura et al., 2016; Shimojima et al., 2016).

Some of the effects of microtubule-related genes on brain asymmetry may be secondary to more general effects on, e.g., age-related cortical thinning. However, enrichment for microtubule-related genes was not reported in a genome-wide association study of bilaterally averaged cortical surface area and thickness measures in 51,665 individuals (Grasby et al., 2020). This suggests a particular involvement of microtubule genes in hemispheric asymmetry rather than bilateral measures. In addition, Sha et al. (2021b) found no significant overlap between genetic variants associated with structural brain asymmetry and genetic variants associated with intracranial volume [the latter were identified in a study of 32,438 participants (Adams et al., 2016)]. This again indicates that the genetic architecture of brain asymmetry is largely distinct from brain size.

SHARED GENETIC EFFECTS ON BRAIN ASYMMETRY AND PSYCHIATRIC TRAITS

As part of their genetic study of handedness in the UK Biobank, Wiberg et al. (2019) tested for genetic correlations between left-handedness and various neurodegenerative and psychiatric traits, making use of publicly available summary statistics from genome-wide association studies of those traits. Genetic correlation indicates the extent to which the same genetic variants, considered in combination all over the genome, are associated with two different traits. Therefore, significant genetic correlation between a pair of traits can indicate a degree of shared etiology. Wiberg et al. (2019) found that left-handedness showed a significant genetic correlation with schizophrenia, which is consistent with an elevated rate of left-handedness in people with schizophrenia (Hirnstein and Hugdahl, 2014). They also found a significant genetic correlation of left-handedness with Parkinson disease, although this may have been disproportionately influenced by the *MAPT* locus mentioned above, due to its unusual genomic properties. *MAPT* mutations are a known cause of frontotemporal dementia with parkinsonism, and various other neurodegenerative diseases can involve aberrant aggregation within neurons of the protein encoded by this gene—microtubule-associated protein *tau* (Strang et al., 2019). This locus may therefore be a particularly likely candidate for having an age-related and/or neurodegenerative effect on brain asymmetry in older adults, in addition to a possible developmental effect on brain asymmetry and handedness.

For the specific genomic loci that Wiberg et al. (2019) found to be associated with left-handedness, they also tested associations with various clinical phenotypes in the UK Biobank. Significant associations for the *MAPT* locus included neuroticism, mood swings, anxious feelings, and miserableness. The *TUBB* locus also showed associations with traits related to anxiety and depression.

In their larger genetic study of left-handedness, Cuellar-Partida et al. (2021) noted that three of the implicated genomic loci had previously been associated with schizophrenia at a statistically significant level, after adjusting for genome-wide multiple testing. At each of these three loci, the allele that increased the odds of left-handedness also increased the risk of schizophrenia. The nearest genes to these loci were *FURIN* that encodes a membrane-bound protease enzyme, *SLC39* that encodes a membrane-bound zinc-influx transporter, and *ABT1* that encodes a transcription activator.

Sha et al. (2021b) used the results from their multivariate genome-wide study of structural brain asymmetry to examine whether genetic loci associated with brain asymmetry are also associated with neurodevelopmental disorders or other behavioral and psychologic traits. When collapsing their genetic association data across multiple variants within individual genes, they found that 43 genes implicated in brain structural asymmetry had previously been reported to associate with educational attainment (Lee et al., 2018), and 15 with intelligence (Savage et al., 2018). Considering common genetic variants across the whole genome in combination, there was statistically significant evidence for a genetic overlap between brain asymmetries and autism, educational attainment and schizophrenia. Since Sha et al. (2021b) had found that brain asymmetry-related genes tend to be especially highly expressed in the embryonic and fetal brain, the genetic overlap between brain asymmetry and psychiatric or behavioral traits may reflect a shared susceptibility to atypical

neurodevelopment in utero. However, shared genetic influences on brain asymmetry and traits such as autism and schizophrenia may also be expressed later, for example, during infancy, childhood, or adolescence.

Although autism and schizophrenia are rare in the UK Biobank general population sample, each individual can be more or less genetically predisposed, based on their genome-wide combination of common genetic variants. In a further study of over 32,000 adult individuals from the UK Biobank (Sha et al., 2021c), polygenic scores for autism and schizophrenia were tested for relations with brain structural asymmetries spanning the cerebral cortex and subcortical structures. Sha et al. (2021c) found that polygenic scores for autism and schizophrenia were weakly positively correlated with each other, and each score was significantly associated with its own distinct set of brain regional asymmetries (Fig. 16.3).

The single regional asymmetry that was noticeably concordant in its associations with polygenic scores for both autism and schizophrenia was asymmetry of the *pars opercularis* surface area. The *pars opercularis* forms part of Broca's classically defined inferior frontal language cortex (Broca, 1861). This region showed reduced leftward asymmetry with higher polygenic risk for both autism and schizophrenia (Fig. 16.3), consistent with leftward asymmetry being the optimal organization to support left-lateralized functions such as language. Therefore, autism and schizophrenia may share an etiologic link through altered structure and function of the inferior frontal language cortex, which would be consistent with impaired social communication in both disorders. Altered hemispheric asymmetry of regions important for language has been proposed to contribute to auditory verbal hallucinations in schizophrenia (DeLisi et al., 1997; Ocklenburg et al., 2015), although with a focus primarily on the temporal rather than frontal cortex (Schijven et al., 2023).

Sha et al. (2021c) found no evidence that the patterns of brain asymmetry associated with polygenic scores for autism and schizophrenia were negatively correlated across brain regions, and therefore the results did not support a concept of autism and schizophrenia as opposing disorders on a single neurobiologic dimension (Crespi and Badcock, 2008; Ciaramidaro et al., 2015). Sha et al. (2021c) also found no evidence that polygenic scores for autism or schizophrenia were associated with more male-like or more female-like average patterns of brain asymmetry, in contrast to what might be expected according to the "extreme male brain" theory of autism (Baron-Cohen, 2002).

The association effect sizes between structural brain asymmetries and polygenic scores for autism and schizophrenia were very small, with multivariate canonical correlations not >0.04 (Sha et al., 2021c). A high degree of statistical significance arose because of the sample size of over 32,000 individuals. It is possible that polygenic dispositions to autism and schizophrenia might show stronger associations with brain measures at levels that are more directly relevant for lateralized functions than macrostructural asymmetries—for example, in asymmetric abundances of certain cell types or gene expression levels.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this chapter, we have seen how recent large-scale studies have enabled the robust identification of genetic loci associated with variation in brain asymmetry and handedness. This has been a major step forward in understanding the genetics of human brain asymmetry. The genes involved tend to be most strongly expressed in the embryonic and fetal brain, compared to brain tissue from later stages of the lifespan. There is a significant functional enrichment for microtubule-related genes. Together, these observations suggest a microtubule-mediated mechanism of left–right axis formation in the developing human brain. Such a mechanism may involve cellular chirality and be distinct from motile cilia-dependent processes of visceral asymmetry development.

However, despite their relatively high expression in the embryonic and fetal brain, many of the implicated genes continue to be expressed at robust levels in the brain throughout the lifespan. Brain structural asymmetry continues to develop throughout the lifespan (Zhou et al., 2013; Roe et al., 2021, 2023), and the UK

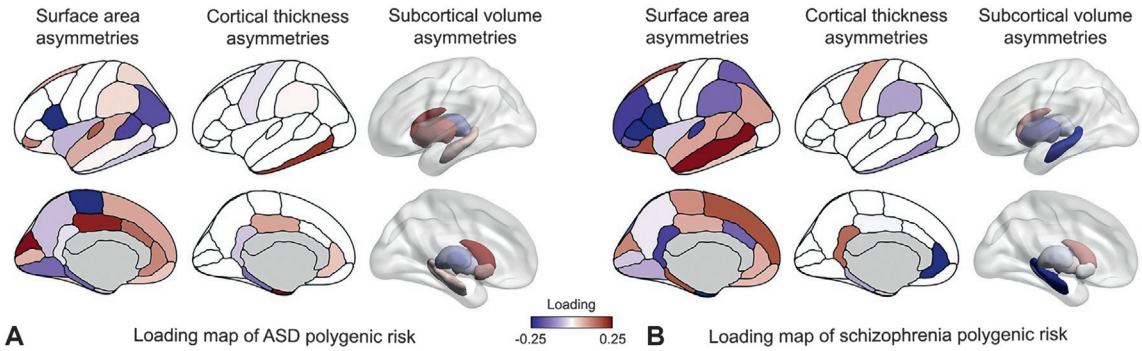

Fig. 16.3. Map of associations of regional brain asymmetries with polygenic disposition to autism or schizophrenia in 32,256 adult individuals from the general population (UK Biobank). Loadings of regional brain asymmetries derived from canonical correlation analyses with (A): autism spectrum disorder (ASD) polygenic disposition and (B): schizophrenia polygenic disposition. A positive loading (red) for a given region indicates a leftward shift of asymmetry associated with increased polygenic disposition. Conversely, a negative loading (blue) indicates a rightward shift of asymmetry associated with increased polygenic disposition. Figure reproduced from Sha Z, Schijven D, Francks C (2021c). Patterns of brain asymmetry associated with polygenic risks for autism and schizophrenia implicate language and executive functions but not brain masculinization. Mol Psychiatry 26: 7652–7660.

Biobank—a mainstay for many of the studies reviewed above—consists of middle-aged to older adults. Furthermore, microtubules are ubiquitous cellular components that are fundamental to many processes throughout cellular life, while many of the genes implicated in interindividual variation in adult brain asymmetry or handedness are not overtly microtubule-related. It is therefore possible that some of the implicated genes exert their influences on brain asymmetry subsequent to neurodevelopment, perhaps by affecting age-related changes in older adults, and neurodegenerative processes.

In order to shed light on these different possibilities, gene-functional approaches will be required, for example, in cellular or animal models. Mice have shown evidence for molecular and neurophysiologic brain asymmetries (Levy et al., 2019; Jordan, 2020) and may be useful as model organisms. One possibility is that microtubule-mediated cellular chirality occurs when the embryonic neural tube is forming and the embryo undergoes axial rotation (Faisst et al., 2002), a process related to left–right asymmetry. Postmortem human embryonic samples are especially rare from this developmental period (2–4 weeks post conception) due to legal and ethical restrictions, which makes studies in model organisms especially important.

Such studies may reveal asymmetry-linked subtypes of genetic susceptibility to psychiatric traits such as autism and schizophrenia, which could contribute to understanding disorder pathogenesis, as well as diagnosis and ultimately personalized treatment. Some forms of these conditions are likely to arise from altered embryonic and fetal neurodevelopment and may be largely irreversible by pharmacologic treatment when diagnosed later in life. Nonetheless, it might still be useful to distinguish such subtypes from drug-tractable forms when making treatment choices. Another crucial question remains on the causal relations that underlie associations between genes, brain asymmetry, and behavior. It may be possible to apply Mendelian randomization (Davey Smith and Ebrahim, 2003), a form of causal modeling suited to cross-sectional genome-wide association data, to understand whether altered brain asymmetries mediate gene-disorder associations.

In the large-scale genetic studies reviewed in this chapter, left-handedness and many regional brain asymmetries were shown to have heritability based on common genetic variants of $<10\%$. At the same time, many of the brain regional population-average asymmetries were substantially different from zero (the point of bilateral symmetry). This overall pattern suggests that developmental mechanisms for brain asymmetry are largely genetically invariant in the population, perhaps due to the negative selection of genetic variants in the genes contributing to brain asymmetry (McManus, 1985; Bishop and Bates, 2019; de Kovel and Francks, 2019). A cytoskeleton-based mechanism of brain left–right axis formation would fit this scenario, because the cytoskeleton is essential for a host of other fundamental functions in cellular biology (Geiger et al., 2001; Janke and Bulinski, 2011). Genetic variation affecting cytoskeletal components may therefore not be well tolerated, for reasons apart from their functions in brain asymmetry.

Twin studies have not found effects of shared environment on brain asymmetries (Guadalupe et al., 2017; Kong et al., 2018), and left-handedness has shown only limited associations with the environmental and early life factors studied so far (de Kovel et al., 2019; McManus, 2021), in which case early developmental randomness may in fact cause most variation in brain and behavioral asymmetries (Mitchell, 2020). Regardless, there is enough heritable variance to have supported successful gene mapping studies, as reviewed in this chapter. Identifying specific genes leads to new insights into trait biology.

Importantly, all of the large-scale studies reviewed in this chapter were based on common genetic variation, i.e., with allele population frequencies of at least half of 1%. This leaves other classes of genetic variation yet to be explored in large-scale studies of human brain asymmetry. For example, rare protein-altering genetic variants may also play a role in interindividual variability. Such variants may have larger effects on brain asymmetry than the common variants studied so far—not necessarily at the population level, but on those rare individuals who carry them. One study in a large consanguineous family with multiple left-handers did not identify such effects using whole exome sequencing (Kavaklioglu et al., 2016). However, an exploratory study of right-hemisphere language dominance—a trait with roughly 1% frequency in the population that occurs mostly in left-handers—found evidence for the involvement of rare variants in genes related to the actin cytoskeleton (Carrion-Castillo et al., 2019). That finding remains tentative as it was based on a sample size below 100. The roles of rare genetic variants in handedness and brain asymmetry may start to be clarified through the recent release of whole exome sequence data in the UK Biobank. [Note added in April 2024: an exome-wide study of rare protein-altering variants in 38,043 left-handed and 313,271 right-handed individuals from the UK Biobank indicated that the heritability of left-handedness due to this class of genetic variant was roughly 1% and implicated another beta-tubulin gene, *TUBB4B* (Schijven et al., 2024)].

The large-scale studies reviewed in this chapter were focused on brain structural asymmetry or handedness. Functional hemispheric language dominance has also shown significant heritability in some studies (Somers et al., 2015; Labache et al., 2020), but large samples for genome-wide association analysis are lacking. The UK Biobank does not have data from language task functional imaging but has resting-state functional imaging, i.e., where intrinsic brain activity was measured without a specific task demand. Correlations of intrinsic activity profiles over time between different brain regions can be used to reconstruct networks or functional gradients that relate to asymmetry of the language network (Joliot et al., 2016; Labache et al., 2023). One study using the UK Biobank data has examined the genetics of functionahl connectivity within the bilateral language network (Mekki et al., 2022) but did not include all left–right homotopic pairs of regions or examine the genetics of hemispheric functional differences. This remains an area for further investigation.

Similarly, the genetics of white matter microstructure and nerve fiber connectivity has been examined in the UK Biobank using diffusion tensor data imaging data (Zhao et al., 2021; Sha et al., 2023), and one of these studies examined connectivity specifically within the core left-hemisphere language network (Sha et al., 2023). However, left–right asymmetry with regard to the contralateral

counterpart regions was not examined. This may be a fruitful avenue for future gene mapping studies of brain asymmetry.

In conclusion, large-scale genetic studies carried out during the last 5 years have greatly advanced our understanding of the genetic contributions to human brain asymmetry. The field now has a substantial list of high-confidence findings to be examined in gene-functional and genetic epidemiologic studies, which may help to understand the roles of the implicated genes in human brain asymmetry and related disorders.

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