CHAPTER

2

Left in the Genes

The majority of humans are right-handed. The estimated 85–90% preponderance of right hand use for one-handed tasks is a worldwide phenomenon. No culture or ethnic group studied has shown a population trend skewed toward the left. However, the left-handed minority persists. Examinations of archeological artifacts indicate that the human group bias toward the right side has existed at least since the era of the Neanderthals (200,000–28,000 years ago), our closest extinct human relative. However, these artifacts also reveal that prehistoric human groups included a left-handed minority. Archeological evidence demonstrates that human ancestors have displayed both right- and left-handedness for millennia [1,2].

Since human handedness is steeped in prehistory, much attention has been focused on its possible genetic determinants. Although non-human primates show handedness at the level of individual animals, humans are unique in showing an extreme majority population bias favoring the right side. Speech and language are also unique human abilities, and the brain centers for language are located in the left hemisphere, the hemisphere that controls the movements of the right hand. Researchers contend that the right hand-left hemisphere language connection accounts for the evolution of a right-handed majority among humans [3].

Since the early years of the twentieth century, researchers have examined handedness patterns among family members and between twin pairs. Based on these studies of people with varying degrees of genetic relatedness, the heritable component of handedness determination is calculated to range from 25 to 40%. Heritability estimates gauge the extent to which genetic differences contribute to the hand use variation found between individuals. Heritability estimates between 25 and 40% indicate that nongenetic factors also make a large contribution to individual variation in handedness. Nevertheless, biologically related individuals should show some similarities of handedness patterns if genes are contributing to the trait [4].

Laterality.
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TABLE 2.1 Percentages of Left-Handed Offspring of Various Parental Handedness Pairings

Parents	Left-handed offspring, %
Both right-handed	11
One left-handed	22
Both left-handed	37

Source: Adapted from: Ref. [5] Porac and Coren, 1981 (Table 5.2, p. 73); Laland et al., 1995 (Table 3, p. 439); and Llaurens et al., 2009 (Tables 1 and 2, p. 883).

Genetic models assume that biological parents and their offspring share 50% genetic similarity. Family studies of handedness examine different parental handedness pairings and the resulting patterns of handedness among their offspring. Of particular interest is the occurrence of left-handedness among the children of left-handed parents. The human left-handed minority has persisted for thousands of years. Therefore, it is reasonable to assume that a gene for left-handedness exists among left-handed mating pairs and its presence accounts for the long-term survival of the left-handed trait. Table 2.1 summarizes data from family studies of handedness. The presence of left-handed parents increases the percentage of left-handedness found among offspring. The occurrence of left-handed children in families with two left-handed parents is more than triple to that found in families where the parents are both right-handed. Adopted children and their adopted parents do not show the resemblance patterns seen in biologically related pairs. This combined evidence bolsters a search for a handedness gene. However, the majority of children of all parental pairings remain right-handed, and family members can resemble each other for reasons not based on their genetic similarities [5,6].

Data from family studies are ambiguous in regard to a nature versus nurture resolution of the origins of handedness. Investigations of the handedness of identical and fraternal twins offer a potential solution to this dilemma. Identical or monozygotic (MZ) twins develop from the same fertilized egg and are assumed to be 100% genetically identical. Fraternal or dizygotic (DZ) twins develop from two separate fertilized eggs and, like other sibling pairs, share 50% genetic similarity. MZ twins are always same-sexed, while DZ twins can be of the same or opposite sex.

The use of MZ twin samples in handedness research has been controversial at times because a subset of MZ twins are mirror-image twins. Their head hair whorls are in opposite directions and their eyedness and handedness are on opposite sides. Mirror-imaging is related to the timing of the division of the single fertilized egg into twins. If the split occurs within 72 h of fertilization, each twin develops its own fetal membrane (classified as dichorionic diamniotic MZ twins); this describes about 70%

TABLE 2.2 Percentages of Concordant and Discordant Handedness Found Among MZ and DZ Twin Pairs

Handedness	Twin type	
	MZ (100% genetic similarity)	**DZ (50% genetic similarity)**
Concordant (RR and LL), %	81	80
Discordant (RL), %	19	20

Source: Adapted from: Ref. [9] Porac and Coren, 1981 (Table 5.3, p. 76); Laland et al., 1995 (Table 4, p. 440); Sicotte et al., 1999 (Table 3, p. 270); Ross et al., 1999 (Table 3b, p. 261); Ooki, 2005 (Table 2, p. 652); Medland et al., 2006 (Table 1, p. 48); Llaurens et al. 2009 (Table 4, p. 884); Vuoksimaa et al., 2009 (Table 6, p. 298).

of MZ twins. If the division occurs later (days 4–7), the twins share one of the fetal membranes but not the other (called monochorionic diamniotic MZ twins). Even later separation results in the twins sharing both fetal membranes (monochorionic, monoamniotic MZ twins). Mirror-imaging effects are associated with delayed embryo splits [7].

In the past, researchers argued that mirror-imaging produces discordant or opposite-side handedness in MZ twins that alters the concordance rates expected between individuals who are genetically identical. The mirror-imaging effect makes MZ twins questionable participants in studies seeking a handedness gene. However, more recent studies find no handedness differences between MZ twins of different membrane types. These results dispel the widely held belief that discordant handedness in MZ twins is caused by mirror-imaging, and it opens the door for the legitimate comparison of MZ and DZ twin handedness. If genes play an important role in the determination of handedness side, then MZ twins, who are genetically identical, should show 100% handedness concordance or at least higher percentages of agreement (right/right and left/left) than DZ twins [8].

Table 2.2 summarizes data from studies of the handedness of MZ and DZ twin pairs conducted since the early years of the twentieth century. A portion of the data in Table 2.2 comes from meta-analyses of existing published reports. A meta-analysis does not collect original data. Instead, the authors analyze the handedness concordance rates reported in other published studies. The handedness concordance of MZ and DZ twins is about equal. This finding presents a problem for simple genetic theories of handedness. The concordance rate between MZ twins is not 100% as predicted by a straightforward genetic process determining handedness. Even if the genetic mechanism is complex, genetically identical MZ twins should show higher degrees of concordance than DZ twins. Neither of these predictions are confirmed by the data in Table 2.2 [9].

Another issue studied in research with twins addresses the question of whether or not twinning is associated with an increased incidence of

left-handedness. The relationship between birth complications and the development of left-handedness is the connection that sparks the interest in twins. The birth of twins as compared to single births is more likely to involve prenatal and birth-related complications. Twins often are of lower birth weight than singletons and are exposed to less optimal uterine conditions, such as crowding. For this reason, researchers consider twins to be a relevant population for examining the role birth stress factors play in increasing the incidence of left-handedness. However, once again, the evidence is mixed. Some twin studies find higher percentages of left-handedness in both MZ and DZ twins when compared to singletons while others do not [10].

Although individual researchers have reached different conclusions, the overall results from both family and twin studies agree in one important way. They support the idea that handedness has a number of determinants one of which is probably genetic. However, other factors both biological and social must be put into the mix of causes. For this reason, proposing a genetic theory of handedness is a complex task that requires a creative approach. Historically, some attempts have been more successful than others at addressing the possible genetics of human handedness.

ONE GENE, TWO HANDS

The human handedness distribution is skewed to the right side. Because the maximum prevalence of left-handedness is only around 10–15% worldwide, geneticists have sought to explain its continuing minority presence in human populations by proposing the presence of a recessive gene among mating groups. Under this framework, the observed handedness or *phenotype* is assumed to be caused by a single gene site with two *alleles* situated on a chromosome. One allele, *L*, causes left-handedness and the other, *R*, right-handedness. An offspring receives one gene from each parent resulting in three different *genotypes* of handedness; these are *RR*, *LL*, and *RL*. *RR* and *LL* individuals have a *homozygous genotype* because the union of gametes at conception results in an identical pair of genes. Alternatively, *RL* individuals have a *heterozygous genotype* because the two alleles at the genetic site are different. Since there are many more right-handers than left-handers, one can further assume that the *R* allele dominates over the *L* allele giving rise to two genotypes with the dominant *R* allele, *RR* and *RL*. These individuals are phenotypically right-handed although their genotype is different. Individuals with the recessive *L* allele genotype, *LL*, are phenotypically left-handed.

Table 2.3 shows the possible offspring genotypes for handedness (assuming four children in each family) that result from the mating of different parental genotypes. The complete dominance of the *R* allele over

TABLE 2.3 Genotypes and Possible Phenotypes in a Dominant/Recessive Single-Gene Model of the Inheritance of Human Handedness

	Genotype			
Mating type	**Father**	**Mother**	**Offspring**	**Offspring phenotypes**
HOMOZYGOUS				
	RR	RR	RR, RR, RR, RR	100% Right-handed
	LL	LL	LL, LL, LL, LL	100% Left-handed
HETEROZYGOUS				
	RL	RL	RR, RL, RL, LL	75% Right-handed
				25% Left-handed
HOMOZYGOUS + HETEROZYGOUS				
	RL	RR	RR, RR, RL, RL	100% Right-handed
	RR	RL	RR, RL, RR, RL	100% Right-handed
	LL	RL	RL, LL, RL, LL	50% Right-handed
				50% Left-handed
	RL	LL	RL, RL, LL, LL	50% Right-handed
				50% Left-handed
HOMOZYGOUS CROSS				
	RR	LL	RL, RL, RL, RL	100% Right-handed
	LL	RR	RL, RL, RL, RL	100% Right-handed

Source: Adapted from Ref. [11] (Table 5.1, p. 71).

the *L* allele can account for why there are many more right-handers than left-handers. Two genotypes with the dominant *R* allele produce a majority of right-handers. A person needs two recessive *L* alleles to display the rarer trait of left-handedness. It is obvious, however, that the predicted offspring outcomes of different parental genotype pairs in Table 2.3 do not match the observed data from family studies shown in Table 2.1. If two left-handed parents are a mating of two recessive *LL* alleles, the entries in Table 2.3 predict only left-handed offspring. Table 2.1 indicates that more than 60% of children of two left-handed parents are right-handed. The overrepresentation of right-handers in families of two left-handed parents poses a problem for a simple dominance/recessive model of genetic transmission [11].

Geneticists make additional assumptions to account for the observed family handedness data. One approach tried in the first half of the twentieth century argues that the *R* allele is not completely dominant over the *L* allele in all circumstances; this is the idea of *incomplete penetrance*.

If the dominant *R* allele is not completely penetrant, then some people will not show right-handedness even though their genotype contains the dominant allele. This situation most likely applies to the *RL* heterozygotes with only one *R* allele and, therefore, a weaker genetic tendency to display right-handedness. To account for the actual handedness patterns in families, geneticists argue that the handedness phenotype is not a direct expression of a genotype. Other factors affect the expression of the dominant *R* allele in heterozygous individuals [12].

These additional assumptions provide a better fit to the observed data. Using the hand preference data listed in the 2013 row of Table 1.2, one can assume that the 80% consistent right-handers are the *RR* genotype; they have a strong genetic shift toward the right hand. The 6% consistent left-handers are the *LL* genotype showing a solid genetic shift to the left hand. The remaining 14% of mixed-handers are the *RL* individuals who have one allele of each type and, therefore, could end up as either right- or left-handed. If 50% of the *RL* people show phenotypic right-hand preference and the other 50% show left-hand preference, one has an 87/13% right/left split in the handedness population. Once assumptions are made about the full or partial expression of the handedness alleles, the predicted outcomes based on genetics are more consistent with actual data [13].

Researchers realized that a simple approach to the genetics of handedness had problems accounting for actual data but the hunt for a handedness gene did not stop. On the contrary, the search for a genetic model to explain the observed percentages of right- and left-handedness in the population as well as the handedness patterns observed among genetically related individuals continued throughout the latter half of the twentieth century. The methodologies used are similar to those of the dominance/recessive genetic model builders. First, propose a genetic mechanism, usually with different alleles, and make assumptions about how the different alleles are expressed phenotypically. Next, derive predictions based on the parameters of the model and compare the values expected by the model to those observed in actual data. If there is no difference between the predictions and the observations, then the model fits. If there is a difference, then modify the genetic model to try for a better fit to the observed data.

Handedness and Brain Lateralization for Language

Humans are asymmetrical. The human heart is shifted toward the left side and the brain centers for control of language functions reside in the left hemisphere. The motor control areas of the left hemisphere also regulate the movements of the right hand. The 1970s saw the development of two genetic theories that included language lateralization in the model. Both approaches deviate from previous research by not arguing for a handedness gene. One of these genetic models has been actively

researched and discussed to the present day while the other failed to gain acceptance by the scientific community and faded away.

The less successful theory is a two gene, four allele model. One gene determines the location of language lateralization with an allele for left hemisphere language dominating over that for right hemisphere localization. The other gene controls the side of handedness. The dominant allele locates handedness on the side opposite or contralateral to the language-lateralized hemisphere while the other allele results in a same-sided or ipsilateral handedness language hemisphere organization. The model results in nine separate genotypes with four possible phenotypes. There are right-handers with language localized in either the right (ipsilateral) or the left (contralateral) hemisphere and left-handers with language in either the right (contralateral) or the left (ipsilateral) hemisphere. Predictions from the model are based on percentage rates of right- and left-handedness and reports of recovery from speech and language disruptions caused by injury to either the right or the left hemisphere. For example, if a person suffers left hemisphere damage from a stroke or other trauma but does not experience language difficulties, language is assumed to be localized in the right hemisphere. The original version of this theory shows a reasonable fit between the model predictions and actual data. However, later researchers, using other data to test the model, found its predictions to be inadequate. The resulting controversy over these discrepant findings led to the eventual demise of this hypothesis [14].

The second approach with greater longevity is the *Right Shift Theory* of Marian Annett. The theory is based on many years of data collection with results published in dozens of empirical papers and two books. It has been researched, assessed, modified, and debated since the 1970's. The model proposes a genetic mechanism that shifts the overall population distribution of handedness toward the right side. Humans do not have a gene that determines handedness but a genetic influence that determines a right shift. If the inherited right shift is present, people are likely to be right-handed. If it is not inherited, then handedness is determined by chance with an equal likelihood of occurrence of right- and left-handedness. This approach implies that right-handedness is determined genetically but left-handedness is not determined genetically [15].

Most genetic theorists use observed hand preference data to test their models. However, Annett bases her theorizing on hand performance. Population distributions of hand performance data are bell-shaped (see Figure 1.2). The genetic right shift factor displaces the peak of this bell-shaped or normal distribution slightly to the right side. Annett proposes a single gene two allele model to explain the right shift. One can inherit either an *RS*+ or an *RS* − allele resulting in three genotypes, *RS*++, *RS*+−, and *RS*−−. The right shift factor advantages localization of language in the left hemisphere and causes a related weakening of the left hand.

The *RS+* allele endows the right shift while the *RS−* allele is neutral for lateralization allowing chance factors to affect both the side of language lateralization and the side of handedness.

This approach provides an explanation for why there is a population bias toward the right side in humans. Evolution has shifted human lateralization to the right side along with advantaging language localization in the left hemisphere. Inheritance of the right shift is the most likely genetic option for humans and, therefore, right-handedness and left hemispheric language prevail. The theory can also explain the presence of right-handed children in families with two left-handed parents. Absence of the right shift factor means that handedness is determined by chance. Thus, children of two left-handed parents, who may be of the *RS−−* genotype, can develop either right- or left-handedness as influenced by these chance factors. Annett's model has had its critics over the years, but even they admit that proposing a genetic code for the presence or absence of asymmetry rather than for the direction of asymmetry is a unique step toward understanding the genetics of handedness development. The introduction of chance influences on the emergence of right- and left-handed phenotypes is another contribution of the theory [16].

Handedness by Chance

Another genetic model developed during this era is that of I. C. McManus. It is similar to the Annett theory in promoting a chance element in the determination of left-handedness. However, the McManus approach claims that there is a single gene with two alleles, *D* and *C*, determining the side of hand preference; this model is not concerned with hand performance. The theory assumes that the *D* (dextral or right) and *C* (chance) alleles are codominant and produce three genotypes, *DD*, *DC*, and *CC*. People with the *DD* genotype have no chance of being left-handed while those with the *CC* genotype have a 50% probability of being left-handed. *DC* genotypes have a probability of left-handedness that is lower, 25%, than the *CC* individuals because of the modifying presence of the *D* allele [17].

McManus demonstrates the adequacy of his model by showing how it can account for both the presence of right-handed children in families of two left-handed parents and the rates of concordance–discordance among MZ twins. For example, the genotype of phenotypically left-handed parents is definitely not *DD*. However, the genotype can be either *DC* (25% probability of left-handedness) or *CC* (50% probability of left-handedness). Even if both parents are *CC* and offspring have only the *C* allele, the children still have only a 50% chance of being left-handed. It is likely that many left-handed parents have the *DC* genotype; their children can have the *D* allele and be either *DC* (75% probability of right-handedness) or even *DD* (100% probability of right-handedness). In an analogous fashion, two MZ

twins with *CC* genotypes each have a 50% probability of being left-handed. Since this chance element applies separately to each twin, the occurrence of left-handedness becomes like two tosses of a fair coin. Sometimes the twins will both toss a head or both toss a tail and have the same handedness, both right and both left. Sometimes one twin will toss a head and the other a tail so one twin is right-handed while the other is left-handed [18].

Another theory with a chance factor claims that there is a single genetic locus with two alleles, *RGHT* or *R* (right) and *r* (random) that determines handedness. There are three possible genotypes *RR*, *Rr*, and *rr*. *RR* and *Rr* individuals are right-handed but the *rr* genotype can be either right- or left-handed with a 50% probability of each. The random determination of the side of handedness in *rr* individuals occurs because they lack the *R* allele and, therefore, lack a consistent right-left asymmetry [19].

A chance factor is also included in the genetic theory of Michael Corballis. His theory has an evolutionary component and also incorporates lateralization of language. This model proposes that at some time in human evolution, a mutation produced a *D* (dextral or right) allele that biased handedness toward the right side and speech lateralization to the left hemisphere. A second *C* (chance) allele is assumed to be neutral in terms of direction of lateralization. These alleles, once again, produce three distinct genotypes, *DD*, *CC*, and *DC*. Corballis accounts for the stability of left- and right-handedness percentages over time by arguing that two alleles can be maintained in a population in stable proportions through a heterozygote advantage. *DC* individuals are advantaged in that they contribute larger numbers of offspring to the next generation when compared to the homozygous *DD* and *CC* genotypes. This advantage maintains the less frequent phenotype of left-handedness within the mating group. The evolution of limb and language lateralization may be linked because it is more efficient biologically to have one hemisphere control both speech and the fine motor coordination of the hands. Evolutionary forces produced the majority bias toward right-handedness and language control by the left hemisphere [20].

Handedness and Sex

Two lines of evidence lead to the idea that handedness is a sex-linked genetic trait. First is the finding of overall higher percentages of left-handedness among males (13%) than females (11%). Second is the discovery of a maternal effect whereby left-handed mothers produce more left-handed offspring than left-handed fathers. Researchers cannot agree, however, on whether the genetic locus for handedness determination is on one or both of the sex chromosomes, X and Y [21].

Figure 2.1 shows the 23 pairs of human chromosomes with chromosomes 1 through 22 called autosomes and the last pair being the sex chromosomes X and Y. Females have two X chromosomes while males

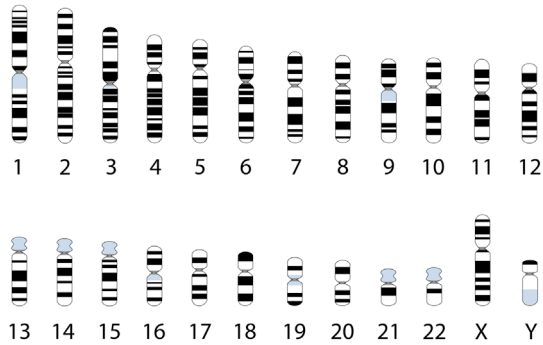

FIGURE 2.1 The twenty-three human chromosomes. The short arm above the center is named p and the long arm below the center is q. The stained bands identify the chromosomes and describe the location of genes. Sections of chromosomes are identified by chromosome number, arm and band. For example, the notation 4p16 is a gene location in the p arm of chromosome 4 at band number 6 in region 1.

have one X and one Y chromosome. Theorists suggest two possibilities. A handedness gene is present on both the X and Y chromosomes in similar regions or it is located on the X chromosome with no counterpart on the Y. Predictions from each of these approaches can be tested using data from families. For example, if a father carries an allele on his X chromosome, he can only pass it along to his daughters while an allele on the Y chromosome can only be inherited by sons. This means that same-sexed siblings in a family should also have the same side of handedness. This prediction has been confirmed by existing data. When geneticists make additional assumptions that there are two alleles *D* and *C* with the latter coding for chance determination of left- and right-handedness or that left-handedness is a recessive gene residing on both the X and Y chromosomes, there is also a fit to existing family data. However, the proposal of a handedness gene on both the X and Y chromosomes remains controversial [22,23].

The family data in Table 2.4, where the handedness of offspring of specific parental handedness pairings is separated for each sex, provide the impetus for arguing that a handedness gene is linked only to the X chromosome. Females have two X chromosomes while males have only one. Therefore, left-handed mothers should produce more left-handed sons than daughters since the son receives his one X chromosome from his mother. Left-handed fathers should produce more left-handed daughters than sons since the son does not receive an X chromosome from his father while a daughter does. This predicted pattern of handedness relationships among parents and offspring is shown in Table 2.4. The data also show the maternal effect. Left-handed mothers in parental pairings of different

TABLE 2.4 Percentages of Male and Female Left-Handed Offspring of Parental Handedness Pairings

Parents		Left-handed offspring, %	
Mother	**Father**	**Males**	**Females**
Right-handed	Right-handed	17	16
Left-handed	Right-handed	25	22
Right-handed	Left-handed	15	21
Left-handed	Left-handed	37	45

Source: Adapted from: Ref. [24] Annett, 2008 (Table 3, p. 116).

handedness produce more left-handed children of both sexes when compared to pairings where the father is the left-hander.

Walter McKeever proposes a three allele, *H1*, *H2*, and *H3* model (*H* stands for handedness) in which males with one X chromosome have three genotypes while females with two X chromosomes have six genotypes. Predictions from his theory produce a good fit to the population percentages of right- and left-handedness and a reasonable fit to family handedness data. His theory has an advantage over others because it does not resort to chance factors determining left-handedness as is the case with the other approaches. However, once again, critics challenge the need to resort to an X-linkage hypothesis. Another theory proposes that an X-linked recessive gene transmission can account for both handedness and the side of language lateralization in the brain [24].

Handedness and the Genome

The search for the genetic basis of handedness is thriving in the twenty-first century. The mapping of the human genome moved researchers beyond models that speculate on a genetic locus for a handedness gene to actual searches of specific regions on individual chromosomes. Genomic research takes several forms. Linkage studies use genetic markers that are segments of DNA with an identified location on a chromosome whose inheritance can be followed. Since genes are segments of DNA, those that lie near each other are likely to be inherited together. Markers are used as tools to track the inheritance pattern of unidentified genes whose general chromosomal location is known. Association analysis looks at the general association of alleles with a given phenotype. Since there are many genes and many alleles, association analysis targets candidate genes that could be associated with a trait. In the case of handedness, for example, a geneticist could look at a candidate gene known to be associated with proteins that play a role in central nervous system development. Genome-wide association studies conduct rapid scans of complete sets of DNA (genome) of large

groups of people to find genetic variations associated with a trait. These investigations use the general paradigm of mapping the genome of participants, measuring their handedness and looking at specific gene locations that might differentiate individuals with different handedness scores [25].

Specific regions of potential influence on handedness determination have been associated with chromosomes 2, 3, 4, 7, 9, 13, 15, 16, 17, and 20 and the sex chromosomes X and Y. These regions do not necessarily contain a gene for handedness. Rather, they are chromosomal locations of molecular genetic mechanisms involved either in brain or in central nervous system development or the development of left–right asymmetry in the human body. For example, there is a condition called *situs inversus* where the internal organs are transposed from their normal positions through the vertical midline of the body. The heart is on the right rather than on the left side and the stomach and spleen are on the right and the liver and gall bladder on the left of the abdomen. Since s*itus inversus* is a homozygous recessive trait, researchers argue that the determination of left–right asymmetries, such as handedness, is likely under the genetic control of chromosomal regions implicated in forming or disrupting asymmetry. These are good places to seek for genes that may influence handedness. It is also possible that humans inherit a tendency toward one type of left–right asymmetry. When that gene is absent, asymmetry is determined randomly. This explains why *situs inversus* is not found in every person with the homozygous recessive genotype [26].

Molecular genetic studies are complex involving many researchers, large databases, and specialized statistical techniques. Also, different studies have used different measures of handedness. Some have tried to find genetic associations to hand performance scores while others have used hand preference measures. Therefore, it is not surprising that this research approach has not produced agreement about individual chromosomal locations significantly associated with handedness scores. A more commonly shared conclusion among scientists engaged in these research efforts is that the genes affecting handedness development are at many genetic locations. As many as 30–40 genetic loci are thought to affect handedness. Even the thinking of single gene theorist, I. C. McManus, has evolved to conclude that predictions about family data based on his single-locus model are similar to those derived from a multilocus approach [27].

MANY GENES, TWO HANDS

The argument that handedness arises from the contribution of many genetic locations (or many alleles) is not new. There are geneticists who have argued for years that handedness is a polygenetic phenomenon where the contributions of many genes add together to affect the outcome of the trait. This approach acknowledges that there are nongenetic

influences on the formation of handedness. The goal is to discover the percentage of overall variation in handedness that is due to additive genetic effects. Polygenetic studies use correlation and regression techniques to make estimates of the relative contributions of nature (genes) versus nurture (environment) to the handedness phenotype.

Assume two groups of biologically related individuals such as parents and their offspring. When measured on handedness, parents and their offspring form two phenotypic distributions of scores. When the handedness scores of parents and their offspring are correlated, one has a measure of whether or not the placement in the two distributions of scores is the same or different for the two individuals. Correlations vary between ±1.0, where + values indicate similarity of placement (both the parent and the offspring are high scorers or low scorers) and − values signify placement differences (the parent has a high score while the offspring has a low score or the reverse). Correlations near zero indicate that the scores of the two related individuals share no systematic relationship. The statistical way of describing a zero correlation is to say that the scores in the parental distribution share no variance with those in the offspring distribution. The closer the correlation is to 1 (either + or −), the more variance is shared between the two distributions and the greater is the ability to predict the offspring score from that of the parent.

The magnitude of the correlations between relatives should be equal to the amount of their genetic similarity if genes are solely responsible for the formation of the phenotype. Parents and their biological offspring, biologically related siblings, and DZ twins share 50% genetic identity. Complete genetic determination of the handedness phenotype should result in a correlation of +0.5 for these related individuals and +1.0 for MZ twins who are 100% genetically identical. Also, the correlations should be positive (+) since one would expect related individuals to be similarly placed in their respective distributions of handedness scores. Unfortunately, correlations of handedness scores between related individuals do not reach these predicted levels. The average parent–offspring, sibling, and MZ twin correlations are close to zero (+0.07, +0.04, and +0.1, respectively). These correlations are far removed from the expected values of +0.5 and +1.0 and suggest that genetic similarities among biologically related individuals do not make much of a contribution to the development of handedness (extracted from Porac & Coren, 1980 (Table 5.4, p. 80); and Tambs et al., 1987 (Table 4, p. 165) [28]).

The ACE of Handedness

Another twenty-first century trend is the use of structural equation modeling to test theories of genetic versus environmental influence in the determination of handedness. Structural equation modeling goes beyond

a simple correlational approach to use predicted versus observed correlations to test models of causality. Researchers devise structural equations that relate the observed handedness of twins to their genotypes and to their environments. They assess the relative importance of the underlying or latent factors of genes and environment by comparing the observed correlations between twins with correlations predicted if different factors are at work to determine the trait. Structural equations in this context take the form of $P = A + C + E$, where P is the phenotype of handedness, A represents the additive impact of the genes that affect handedness, C stands for environmental influences that are common to the two twins, such as socioeconomic status, diet, or peer influences, and E represents the role of unique environmental effects that the twins do not share such as differential parental treatment or accidents. One can coin the term *ACE* modeling for this approach.

The predicted correlations for MZ and DZ twin pairs differ for A. MZ twins at 100% genetic identity have a predicted A correlation of +1.0 while that for DZ twins with 50% genetic identity is +0.5. MZ and DZ twins share the predicted correlation of +1.0 for the C or common environment component and zero for E or the unique environment component of the model. These predictions are diagramed in Figure 2.2. Researchers can estimate E because handedness differences between MZ twins can only arise from the influence of the environmental component of the model that is unique to each twin. An estimate of A is found by looking at the degree to which MZ twins are more similar to each other than DZ twins. Since MZ twins are genetically identical, the correlations between their handedness scores should be higher than that found between DZ twin

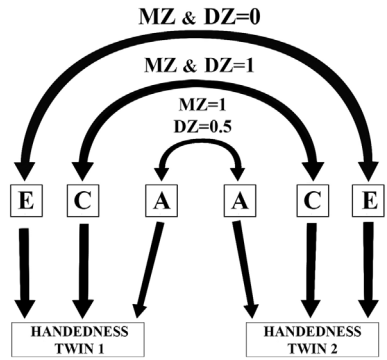

FIGURE 2.2 Predicted correlations between MZ and DZ twins for the genetic component, A, the common environment component, C, and the unique environmental component, E, in the *ACE* model approach to study human handedness. *Source: Adapted from: Ref. [29] (Figure 1, p. 121).*

pairs. Assuming that the effect of a common environment is similar for MZ and DZ twins, then *C* is derived from the difference between the MZ correlation and the *A* or genetic estimation [29].

Studies using structural equation modeling to estimate the *ACE* components for determination of the side, right or left, of handedness find, on average, that the *A* or genetic component accounts for only 17% of the variation in handedness scores between twins. The *C* or common environment component contributes 0% so the remaining 83% is attributed to the *E* or unique environment factor. Seventeen percent is a lower estimate of genetic influences on the development of handedness than given by the more traditional heritability estimates mentioned at the start of the chapter (25–40%). One study could not find a variant of the *ACE* model that provided a good fit to data on the side of handedness. The researchers applied the model to handedness consistency data, how strongly a person shows right- or left-handedness and found the best fit for a model that contained only the *C* (12%) and *E* (88%) components. This model fit does not contain a genetic element [30].

WHAT CONCLUSION IS LEFT?

This chapter summarizes a century of work on the genetic basis of handedness. Several *facts* can be gathered from this enormous research effort. Simple genetic models of handedness determination have been abandoned. Researchers agree that there is a biological basis to handedness that most likely includes a genetic component, and genomic mapping allows them to search for contributing genes on specific chromosomes. There is an emerging consensus that the result of these efforts may not be the discovery of a gene for handedness. Rather, the development of the handedness phenotype is likely influenced by many genes that may also operate to determine the arrangement of body asymmetries and/or brain development and lateralization. Another emerging consensus acknowledges that nongenetic factors, both biological and environmental, are involved in the development of handedness within individuals. It is *fiction* to think researchers will agree. The debate over whether a gene affecting handedness is on the X and Y chromosomes or on chromosome 2 has been vigorous. The genomic search for a handedness gene is energetic and ongoing, so one can expect more such disputes in the future. A reasonable conclusion regarding the current state of the genetics of handedness is that a gene or genes influencing handedness probably exist somewhere on the genome and someday the location(s) will be discovered [31].

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