

Human Handedness and Scalp Hair-Whorl Direction Develop From a Common Genetic Mechanism

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ABSTRACT

Theories concerning the cause of right- or left-hand preference in humans vary from purely learned behavior, to solely genetics, to a combination of the two mechanisms. The cause of handedness and its relation to the biologically specified scalp hair-whorl rotation is determined here. The general public, consisting of mostly right-handers (RH), shows counterclockwise whorl rotation infrequently in 8.4% of individuals. Interestingly, non-right-handers (NRH, *i.e.*, left-handers and ambidextrous) display a random mixture of clockwise and counterclockwise swirling patterns. Confirming this finding, in another independent sample of individuals chosen because of their counterclockwise rotation, one-half of them are NRH. These findings of coupling in RH and uncoupling in NRH unequivocally establish that these traits develop from a common genetic mechanism. Another result concerning handedness of the progeny of discordant monozygotic twins suggests that lefties are one gene apart from righties. Together, these results suggest (1) that a single gene controls handedness, whorl orientation, and twin concordance and discordance and (2) that neuronal and visceral (internal organs) forms of bilateral asymmetry are coded by separate sets of genetic pathways. The sociological impact of the study is discussed.

HANDEDNESS has been extensively studied in the past century, but its exact cause remains debatable (PERELLE and EHRMAN 1983; BISHOP 2001). The debate starts with the definition of handedness. Although a layperson knows about hand preference, all studies must first assess the parameters of handedness. This is because the inclination to use one hand over the other for certain tasks is biased due to culture. Studies that monitor only a single trait, such as writing-hand use, to determine the cause of handedness are flawed, because the practice of writing is a learned behavior; consequently, hand preference can be culturally influenced. Such a cultural bias greatly blurs the issue for determining the exact cause of handedness.

One of the best definitions of handedness was used in a study done in North America by D. C. Rife (RIFE 1940), whose definition took such cultural biases into consideration. According to this stringent definition, individuals are considered right-handed (RH) if they prefer to use the right hand to throw a ball, use a spoon, saw, sew, shoot marbles, bowl, cut with a knife, cut with scissors, hammer, and write. If they routinely use the left hand or either hand for any number of these 10 tasks, they are designated non-right-handed (NRH). Thus, both left-handers and ambidextrous individuals are pooled as NRH. This definition seems to compen-

sate for cultural bias for individual tasks. We previously used Rife's definition to calculate the allele frequency (KLAR 1996); the same definition of handedness is used in this study for better comparison between results of this study with an earlier one. As other studies have used different criteria, controversial stances of different investigators are expected. Following different definitions, the prevalence of NRH in different studies varies from 9 to 11% (RIFE 1940; PERELLE and EHRMAN 1983; CORBALLIS 1991).

The contribution of genetics in handedness has been supported by studies of families of concordant twins and adopted individuals (LEVY and NAGYLAKI 1972; ANNETT 1985a; McMANUS 1985; KLAR 1996; CORBALLIS 1997). However, because the Mendelian mode of inheritance has not been demonstrated for handedness, psychologists have not accepted the purely genetic mechanism. Rather, a major school of thought proposes that handedness is primarily, or at least partially, a learned behavior (COLLINS 1977; CORBALLIS and MORGAN 1978; COREN 1992). Other environmental factors, including brain damage resulting from stress during birth (BAKAN *et al.* 1973; PERELLE and EHRMAN 1983), or a surge of fetal testosterone level during pregnancy (GESCHWIND and GALABURDA 1987), are additional mechanisms that have been proposed. However, evidence for such theories is lacking. A recent study proposed a gene-culture coevolution model (LALAND *et al.* 1995). In this model, selection is thought to have eliminated all genetic variation contributing to handedness such that all individuals

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are predisposed to be RH, but cultural influences dictate their hand use; in short, only the individual's upbringing determines handedness.

Studies favoring the cultural model of handedness present three major arguments against the purely genetic model. First, hand use of some individuals had been culturally changed. Second, up to one-half of the children born to left-handed (LH) \times LH parents are RH (RIFE 1940). Third, and probably most importantly, 18% of individual members of monozygotic (MZ; "identical") twins are discordant (*i.e.*, one twin RH and the co-twin NRH), despite sharing the same genes (RIFE 1940; BOKLAGE 1981). Because of these arguments, combined with the major disagreements among proponents of the earlier genetic models postulating vastly different allele frequencies controlling handedness (ANNETT 1985a; MCMANUS 1991), researchers often consider handedness to be a classic "complex trait" that is specified by a combination of genetics and environmental causes. Understandably, psychologists have not accepted the prevailing single-gene genetic models (ANNETT 1985a; MCMANUS 1985; KLAR 1996). Indeed, more recent studies on the subject also conclude that genes do not play a significant role in handedness (BISHOP 2001; JAMES and ORLEBEKE 2002). Thus, both environmental and genetic models have been proposed to explain the etiology of human handedness. So far no locus attributed to handedness has been mapped (FRANCKS *et al.* 2002; VAN AGTMAEL *et al.* 2002) and the field remains controversial. Certainly, multiple points of view exist and a consensus has not been achieved thus far, despite a long-time interest in and much literature published on the topic.

Indeed, the debate regarding the cause(s) of handedness is a classic example of the controversy over the relative importance of "nature" (biological endowment) *vs.* "nurture" (environment and culture) on human behavior. It seems that tests more definitive than the ones employed earlier are required to differentiate between these models. This study tested and satisfied three key predictions of a genetic model by conducting two independent lines of investigations. Individuals of the general public and the progeny of handedness-discordant twins were investigated. On the basis of this work, we advance a conclusion opposite to that of an earlier study involving hair whorls. This study unequivocally indicates a "nature" explanation in specifying handedness.

RESULTS

Rationale for differentiating between nature and nurture models: The controversy over the causes of handedness has probably deterred gene-mapping investigations. Generally, the result of genetic mapping of the handedness-determining gene(s) would be the most convincing evidence favoring genetic etiology. Often in

practice, however, clear genetic evidence indicating the number of genes involved is required before formal gene-mapping studies are initiated. Lacking such information, and directed crosses of humans being out of the question, we chose an altogether different strategy. With the goal of distinguishing between nature and nurture mechanisms, this study was initiated to examine an association of handedness with the development of some other human body feature, *viz.* a feature (1) that exhibits left-right body axis asymmetry and (2) whose development is strictly biological and not culturally influenced. Such associations for handedness with left- *vs.* right-foot or eye preference have been partial (SEARLEMAN 1980). In addition, these traits are subject to cultural intervention. Consequently, results of studies of these traits have not been decisive in settling the controversy.

The most prominent genetically determined left-right asymmetry is that of visceral organs. Almost all (~99.999%) individuals develop with the heart placed on the left side of the chest cavity, the spleen on the left side of the abdomen, the two-lobed lung on the left side, and the three-lobed lung on the right side (KLAR 1994; HAMADA 2002). Because both RH and NRH develop with the standard visceral orientation, functional asymmetries of the brain, including handedness, are clearly not coupled with visceral organ asymmetry. Fortunately, another feature—scalp hair whorl rotation—exists that shows radial as well as the left-right asymmetry. The whorls show clockwise or counterclockwise rotation in most individuals (WUNDERLICK and HEEREMA 1975). Data on possible association between the direction of whorl rotation and handedness are presented here even though an earlier study suggested that these traits do not appear to derive from a common mechanism (COLLINS 1977). Only reports of individuals with a single hair whorl showing clear rotation are included. For obvious reasons, information on individuals who are bald, lack a hair whorl, have multiple whorls, or have long hair is not incorporated in the analysis.

A test of the genetic model: the general public (mostly RH) exhibits predominantly clockwise, but NRH show a random-coiling pattern: In the relatively recent genetic "random-recessive" model, it was proposed that a single, dominant, 100% penetrant, *RGHT* (for *Right*) gene causes one to become a RH individual; its recessive and nonfunctional allele, *r* (for *random-handed*), in the *r/r* homozygote confers a statistically random chance, an equally likely 50:50 chance for the individual to become either RH or NRH (KLAR 1996). It was further speculated that the *R* (for *RGHT*) gene causes the left-cerebral hemisphere to develop into a "dominant hemisphere," so defined where language is processed; and its second function is to couple the dominant hemisphere to the development of RH preference. Consequently, the model predicts, first, a strong positive association between these attributes in RH individuals (of suggested



FIGURE 1.—Hair whorls. The counterclockwise parietal scalp hair-whorl on the left is of a NRH person, and the one on the right of the RH author swirls clockwise.

R/R or *R/r* genotype) and second, their random distribution with respect to each other and in relation to the left *vs.* right side of the body in NRH (*r/r*) individuals. By this logic, other similar predictions of the model can be economically tested using a noninvasive and definitive method by simply examining the rotation of hair whorls on the scalp if the NRH individuals develop coiling. Direction of coiling is an easy phenotype to score: Figure 1 shows clockwise and counterclockwise examples of hair whorls.

Predominantly clockwise whorls were reported in 93.8% of 404 newborns investigated in a study done in the United States (WUNDERLICK and HEEREMA 1975). Because that study was limited to newborns, it was not designed to investigate the association of hair-whorl rotation with handedness. Confirming that finding of nearly three decades ago, we observed clockwise whorls in 91.6% (458 among 500 individuals; Figure 2) of the general population, consisting of individuals of all ages and of both sexes, and residing primarily in the state of Maryland. Due to a large sample size, collecting the data on their handedness as well as sex was impractical. But collecting information on hair-whorl rotation of such a large sample is essential to get statistically significant results. The subjects were unobtrusively observed for their hair-whorl patterns by visiting the local shopping malls. These data provide the prevalence of clockwise rotation in the population at large. Because the predominant proportion of individuals in the general population both in our sample and in an earlier study (WUNDERLICK and HEEREMA 1975) are expected to be RH (RIFE 1940; PERELLE and EHRMAN 1983; CORBALLIS 1991), it follows that most RH exhibit a clockwise pattern.

The key prediction of the random-recessive model is that the traits of handedness and the scalp hair-whorl rotation should be uncoupled in NRH individuals such that one-half of them should exhibit a counterclockwise pattern. Indeed, the most informative result is that among 49 NRH individuals surveyed, mostly from participants of an earlier handedness study (KLAR 1996), 27

showed clockwise and 22 showed a counterclockwise pattern (Figure 2). Remarkably, the NRH individuals showed a 5.3-fold increase in counterclockwise rotation relative to the value found in our sample of the general public. Clearly, first, this 44.9% counterclockwise rotation in NRH is hugely different from the 8.4% level found in the general population. Second, the result is statistically consistent with the 50% NRH prediction of the random-recessive model ($\chi^2 = 0.51$, d.f. = 1, $P = 0.475$).

The second test: one-half of individuals showing counterclockwise hair rotation are NRH: From the results presented above, and according to another prediction of the model, it follows that among individuals chosen only because of their counterclockwise rotation, one-half of them should be NRH. In contrast, only 9–11% of individuals are NRH in the general population (RIFE 1940; PERELLE and EHRMAN 1983; CORBALLIS 1991). To test this prediction, another independent sample of individuals was surveyed. Interestingly, of 23 participants with the counterclockwise rotation examined, 12 were RH and 11 were NRH. This observation satisfies the second key prediction of the genetic model.

Because most individuals in the general public develop a clockwise pattern that develops biologically and that is clearly not a culturally influenced trait (WUNDERLICK and HEEREMA 1975; this article), it can be con-

Rotation	General public	NRH
Clockwise	458	27
Anti-clockwise	42	22
% Anti-clockwise	8.4	44.9
Fold-increase	-----	5.3 X

FIGURE 2.—Comparison of directionalities of hair-whorl rotation of NRH individuals with the general public. The numbers represent the numbers of individuals in each category.

cluded that the direction of coiling is determined genetically. If it were not genetically specified, a default mode for not making a decision at a binary choice should cause 50 clockwise:50 counterclockwise mixtures, much like the 50 clockwise:50 counterclockwise patterns of scales on pinecones (KLAR 2002) and analogous to the statistical head *vs.* tail outcome of a coin toss.

It should be pointed out that the finding that the general population, consisting mostly of RH individuals, preferentially exhibits a clockwise rotation (WUNDERLICK and HEEREMA 1975; this article; Figure 2) does not address the question of the etiology of handedness because such an association could be unrelated. These features might have developed by different mechanisms, such as hair rotation by genetics, handedness by an unrelated genetic pathway, or by learning. But, if genetics were not the cause for handedness, or if handedness develops from a different genetic mechanism, NRH individuals would also exhibit predominantly a clockwise rotation. Instead, NRH showed a random mixture of hair patterns. This finding is confirmed by another independent result: Individuals investigated because of their counterclockwise rotation were found to be NRH in about one-half (11 of 23) of the cases. Therefore, these two results establish that, like whorl rotation, handedness is a genetically determined trait. Thus, it is an inescapable conclusion that hair-whorl direction and handedness share a common genetic mechanism.

The results also suggest that the putative *R* gene does not function to cause whorl coiling. Rather, the *R* gene dictates nonrandom distribution of handedness and whorling traits only with respect to the left-right body axis. Consequently, the *R/R* and *R/r* individuals develop as RH, exhibit clockwise hair coiling, and presumably have a dominant left-brain hemisphere. Correspondingly, the individuals with the putative *r/r* genotype do develop laterality features, but their distribution with respect to each other, and to the left *vs.* right side, is random. In contrast, COLLINS (1977) concluded that there seems to be no association between the directionalities of handedness and hair coiling, and thus they appear not to be derived from a common mechanism, genetic or otherwise. However, in earlier studies conducted in different human generations, varied definitions of handedness—different from the definition used here—were used, often based only on the single writing-hand criterion. More importantly, Collins' analysis did not entertain the idea of uncoupling of both handedness and hair-whorl rotation with respect to each other as well as to the left-right body axis in NRH individuals, thus resulting in a conclusion opposite to that of this study. As usually expected, if all NRH individuals were to develop only counterclockwise coiling or exhibit no coiling, this debate probably would have been settled a long time ago. Interestingly, the situation with handedness is exactly analogous to a single-gene recessive mutation described back in 1925 that caused unilateral spot-

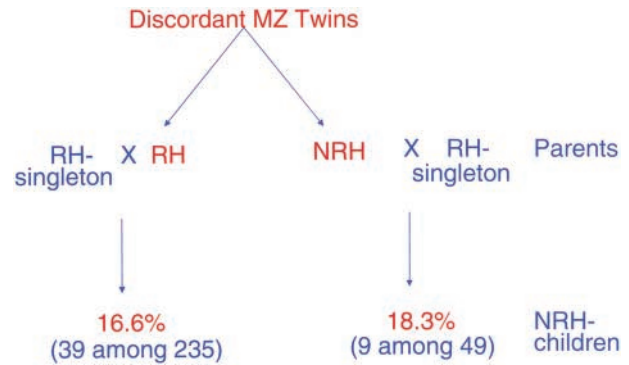


FIGURE 3.—Twins' progeny. The percentages of NRH children born to discordant MZ twins who were married to RH singletons are presented. The numbers of children surveyed are indicated in parentheses.

ting of elytra of the *Bruchus quadrimaculatus* to produce an equal number of “dextral-” and “sinister-”spotted beetles (BRETENBECHER 1925).

The third test: RH members of handedness-discordant twin pairs produce a higher percentage of NRH children, a result similar to that of the standard NRH parents: As mentioned in an earlier section, a central argument against the genetic etiology for handedness is the very well-emphasized feature of discordance observed in 18% of MZ twins (RIFE 1940). According to the usual expectation of a genetic model, co-twins in each pair should always have the same handedness—both being either NRH or RH—because co-twins have identical genes. In contrast, it was hypothesized in the random-recessive model that discordance would result from the randomness of hand preference in only those twins who have the *r/r* genotype (KLAR 1996). We genetically tested this hypothesis that predicted *r/r* constitution of discordant twins. Specifically, we determined the hand use of children of twin families in which one of the parents was a discordant RH twin (because their co-twin was known to be NRH) and the other parent was a conventional single-born (singleton) RH. The genetic model predicts 19.5% NRH children, as was reported for singleton NRH (predicted *r/r* genotype) \times RH matings (RIFE 1940), but the psychology (culture) model predicts that these matings should produce 7.6% NRH children, as was reported in singleton RH \times RH families (RIFE 1940). These expectations are based on the 61% *R* and 39% *r* allele frequency calculated earlier for RH singletons (KLAR 1996).

In a sample surveyed from the MZ twins participating in the Minnesota Twin Registry, we found that the discordant RH twin \times RH crosses produced 16.6% NRH progeny (Figure 3). This value is significantly different statistically from the 7.6% prediction of the psychology model ($\chi^2 = 27.0$, d.f. = 1, $P < 0.001$), but not significantly different from the 19.5% prediction of the genetic model ($\chi^2 = 1.26$, d.f. = 1, $P > 0.20$). This result argues against the psychology model for discordant

twins and satisfies a crucial prediction of the genetic model for both handedness and twins' discordance. A related result is that the NRH discordant twin \times RH crosses produced a similar number of 18.3% NRH progeny (Figure 3); however, this result is not at all informative to distinguish between the primary models under consideration because both models predict the same outcome. To our knowledge, this is the only study to investigate the handedness of the progeny of discordant twins.

The result of discordant twins also helps to differentiate between different genetic models. The findings of association between handedness and scalp hair-whorl rotation support all models (LEVY and NAGYLAKI 1972; ANNETT 1985a; McMANUS 1985; KLAR 1996), positing genetics as the cause of handedness. But this observation does not provide information as to which genetic model should be favored. Interestingly, the result with twins is helpful in addressing specific features of various genetic models. One such model involves two genes, each gene with two alleles, where one locus determines the lateralization of speech capacity in the brain, and the second decides contralateral *vs.* ipsilateral control of the preferred hand (LEVY and NAGYLAKI 1972). However, the existence of discordant twins argues against this model, because only concordant pairs are predicted (BOKLAGE 1981). Also, the proposal of this model as well as other theories postulating discordance due to brain damage from "birth stress," "mirror imaging," or a surge of fetal testosterone level during pregnancy (BAKAN *et al.* 1973; PERELLE and EHRMAN 1983; GESCHWIND and GALABURDA 1987) is inconsistent with our result of discordant twins being genotypically similar to NRH individuals, rather than to those of the general population. Such theories for NRH singletons are ruled out as well by the result of association between handedness and whorl rotation (see above).

Similar to the random-recessive model, two earlier models involving a single gene with two alleles hypothesized random handedness in homozygotes of the minor alleles. However, unlike the random-recessive model postulating a 100% penetrant and fully dominant *R* allele and a recessive null *r* allele, the ANNETT (1985a,b) and McMANUS (1985) models proposed an additive effect of varying degrees of both incompletely dominant alleles, so that a significant percentage of heterozygotes would also develop as NRH. Furthermore, the Annett model is a conventional threshold model positing a continuously varying characteristic and it further postulates that even rs^+ (right-shift)/ rs^+ homozygotes will develop to be NRH, albeit at a low frequency. ANNETT (2002) has also pointed out salient differences between these three single-gene models. Incidentally, the proposal of additive effects has been pointed out to make it very difficult to map the handedness locus by following the segregation of molecular markers in families (VAN AGTMAEL *et al.* 2002). In addition, Annett explained MZ

twins' discordance by proposing reduced expression of the hypothesized rs^+ allele only in twins by an unknown mechanism. McManus also proposed discordance due to chance alone, in *C* (for Chance)/*C* homozygotes as well as in a significant number of *D* (for Dexter)/*C* heterozygotes, which occurs independently in each MZ twin. Instead, our finding of the progeny of twins suggests that discordant twins are genetically recessive homozygotes, a result inconsistent with the Annett and McManus models.

In summary, the results of this study, combined with an earlier finding that the RH children of LH \times LH parents possess a genotype similar to that of the NRH individuals (KLAR 1996), favor the random-recessive model. Furthermore, the number of 7.6% NRH children born to RH \times RH parents (RIFE 1940) was neatly explained previously by the allele frequency derived from applying the random-recessive model to the handedness study (KLAR 1996). As pointed out by BOKLAGE (1981), another result consistent with the genetic explanation for discordant twins is that parents and sibs of discordant twins are twice as likely to be NRH, when compared with the general population (RIFE 1950). In addition to handedness, the 58 *R*:42 *r* allele frequency in the public at large explains the proportion of counter-clockwise swirling observed in the general population by proposing a random coiling of *r/r* homozygotes and the clockwise pattern of *R/R* or *R/r* individuals.

Since GALTON's (1876) original suggestion, discordant MZ twin pairs have been extensively investigated to differentiate the effect of genes *vs.* the environment on human behavior. Most studies with discordant twins, including those with handedness (TAMBS *et al.* 1987; JAMES and ORLEBEKE 2002), have been concluded to favor the significant influence of environment on the trait. In contrast, our findings explain handedness discordance due to random choice operating in individual twin members owing to their *r/r* genetic constitution.

The nature-nurture debate for handedness is not just of academic interest. Fundamental questions of great importance in neurobiology are (1) how do the brain hemispheres acquire different cognitive functions, and (2) what is the etiology of human variations in cerebral organization? Central to these questions is the explanation of the so-called "complex correlation" of brain hemisphere specialization and handedness. Therefore, for defining the mechanism of brain hemisphere lateralization concerning the distribution of cognition, probably the most experimentally amenable avenue is to determine the cause of handedness.

The two hemispheres of the brain morphologically seem to be mirror images of each other, but interestingly they perform very different cognitive functions. Also, the left hemisphere controls the right side of the body and vice versa. Nearly 97% of RH individuals localize speech, logic, and language processing in the left side of the brain, the so-called "dominant hemisphere." The

“automatic hemisphere” on their right side processes emotional information including intuition, feelings, art, and creativity. In contrast, the respective split varies in different studies from $\sim 50:50$ (GOODGLAS and QUADFASAL 1954) to 70:30 (COREN 1992) in LH individuals. This variation perhaps results from employing different definitions of handedness in disparate studies. All three single-gene models (ANNETT 1985a; MCMANUS 1985; KLAR 1996) concerning handedness propose that the function of the dominant allele is to localize speech capacity to the left hemisphere and couple it to the development of the dominant hand on the contra-lateral right side. In fact, ANNETT (1985a) calculated the handedness allele frequency from patients with loss of speech due to damage in one hemisphere of the brain and from the incidence of left-handedness with right-hemisphere dominance. Interestingly, the calculation of 58% dominant *R* and 42% recessive *r* allele frequency directly from a handedness study (KLAR 1996) is remarkably similar to that of the rs^+ and rs^- alleles derived by Annett. Because MCMANUS (1985) proposed a pronounced additive effect of alleles in *D/C* heterozygotes to produce 25% NRH—an additive effect much higher than that proposed in the Annett model—his calculation of 15.5% *C* and 84.5% *D* allele frequencies is highly different from those of the Annett and the random-recessive models. Although lateralities of brain hemisphere and handedness can now be assumed to result from genetics in healthy individuals, young patients with one injured hemisphere do develop language capacity in the remaining hemisphere. Thus, the brain shows considerable plasticity for development of language capacity in young children.

In contrast to the abundance of studies regarding handedness, very few studies have investigated correlation of language lateralization with hand preference especially with monozygotic twins. Relatively recently a study applied the dichotic listening paradigm to investigate correlation of handedness with language lateralization in twins and concluded that language lateralization is nongenetic in origin (JANCKNE and STEINMETZ 1994). However, because in the pooled sample 10 of 20 twin pairs investigated were handedness discordant, this lack of correlation is easily explained by the genetic model as the language lateralization is supposed to be random in discordant pairs. Recently, SOMMER *et al.* (2002) found an imperfect intrapair correlation (0.74) of language lateralization in the RH concordant twins, but not in the handedness-discordant group. Thus, this twin study partly supports a genetic basis for handedness, but information on the number of genes involved cannot be derived from such an analysis. Significantly, in the handedness-discordant twin pairs, 7 of the 13 LH twins developed right cerebral dominance. The twinning process itself was postulated to cause variation of handedness-discordant twins (SOMMER *et al.* 2002). However, we advance an alternate explanation based on the random-

recessive model whereby the distribution of brain laterality is random due to the *r/r* genotype of discordant twins. We predict that a similar random distribution will be found in LH concordant twins, but such twins were not included in that study. The genetic etiology for handedness in twins is also supported by a recent structural study of the brain: Both handedness-discordant twin members and NRH singletons showed no significant brain hemisphere asymmetry in the temporal and frontal brain regions, in contrast to the concordant RH pairs and RH singletons, which demonstrated significant asymmetry (GESCHWIND *et al.* 2002).

DISCUSSION

The findings of coupling between handedness and hair-whorl rotation in the general public and their decoupling in NRH clearly establish genetics as the cause of handedness, while the findings on the progeny of discordant twins favor a single-gene/locus model. This evidence should provide impetus for future studies for mapping the hypothesized handedness gene. This is a pressing issue as it has been suggested that the debilitating illnesses of schizophrenia and bipolar affective disorders may result from developmental anomalies of cerebral asymmetry (FLOR-HENRY 1969; BOKLAGE 1977; ANNETT 1985a; MCMANUS 1985; CROW 1990; KLAR 1999).

The biology of development of neuronal and visceral bilateral asymmetry: The data in the current study help to answer an unrelated question of whether visceral and neuronal forms of bilateral asymmetry are coded by one or more sets of genetic pathways. As stated in an earlier section, the most prominent genetically specified case is that of visceral laterality (KLAR 1994; HAMADA 2002). How could it be that handedness and hair-whorl rotation are coupled due to genetics (this study), but neither trait is associated with visceral lateralization although all three traits relate to the same left-right body axis? To reconcile this paradox, we hypothesize that one genetic pathway controls the neuronal system lateralization concerning handedness, brain hemispheres, and hair-whorl rotation, and another independent pathway(s) specifies visceral lateralization (Figure 4). In this regard, it is helpful to realize that the visceral organs develop from the endoderm and mesoderm layers of embryonic cells, while the scalp epidermis, brain, and the nervous system develop from the ectoderm layer. Furthermore, we imagine that these pathways independently derive cues for their development from the dorso-ventral body axis. Therefore, we speculate that parallel genetic pathways must have evolved to develop alternate forms of bilateral asymmetries and that they probably execute their function after meso-, endo-, and ectoderm layers of cells in the embryo have already formed. This proposal raises many interesting questions for future studies, such as how the symmetry in the embryo is broken initially and how the sidedness is determined (KLAR 1994, 1999;

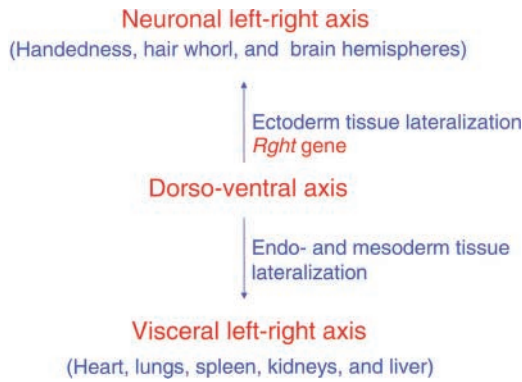


FIGURE 4.—A summary of hypothesized independent genetic pathways for left-right axis determination of visceral and neuronal organs. Both pathways in humans are proposed to derive cues for their respective left-right axis development from the dorso-ventral body axis. The hypothesized *RGHT* gene is proposed to function for ectoderm tissue lateralization. Analogous functions for visceral lateralization have been identified from model organisms such as mice, chick, and *Xenopus* (HAMADA 2002).

HAMADA 2002). One hypothetical way this might be accomplished is by nonrandom segregation of “Watson” *vs.* “Crick” chains of parental chromosomes to progeny cells at a certain cell division during embryogenesis (KLAR 1994, 1996), a mechanism analogous to the distribution of developmental asymmetry between sister cells of fission yeast (KLAR 1990).

The sociology of handedness: As instances of clearly genetically inherited human behavior are few, the hand preference may be an interesting example. It is expected that this study should settle the unending nature-nurture debate for handedness in favor of nature. No doubt the expression of handedness itself is subject to social influences; however, the primary cause is evidenced here to be genetic. Therefore, we suggest that humans are born with hand preference that is prenatally determined. This work should also impact the social aspects of handedness. With this knowledge, it should be possible for the parents to predict that their newborn with a counterclockwise hair whorl will develop into a left-handed or ambidextrous person in 50% of the cases. Furthermore, all individuals with the counterclockwise rotation are expected to be of the *r/r* genotype and this information should be helpful in selecting families for mapping the predicted handedness locus and for easily and more precisely determining the allele frequency in different human races. In this context we note that ANNETT (1985a) reported the percentages of clockwise hair whorls as 65% ($n = 209$) for RH and 62% ($n = 26$) for LH in undergraduate psychology students from the United Kingdom. These values are considerably different, especially for RH, both from those of this study and from that of WUNDERLICK and HEEREMA (1975) concerning the U.S. public at large. Other than possible variation due to different races investigated, varied

definition of handedness as well as selection of the particular section of the public may have resulted in differences in the percentages of hair whorl orientation. In future studies it will be interesting to clarify the reason for this disparity. Meanwhile, respecting their natural tendency, a proportionate number of “lefty” tools should be made readily available for this largest minority of LH persons. Last, now knowing that nature (*i.e.*, genetics) determines handedness, should the ways of those cultures discouraging left-hand use, including the use of derogatory terms such as “sinister” or “gauche” to describe LH, be questioned?

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