
Gastropods as an Animal Model for Studying Autism and Other Behavioral Phenotypes

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Abstract

Gastropods have an unusual genetic mechanism in which the mother's genotype determines the shell phenotype of her offspring. Experiments have shown that these unknown, maternal-effect genes determine shell chirality, the direction each snail shell coils, with dextral or right handed having a clockwise spiral, and sinistral or left handed having a counterclockwise spiral. Most snail species consist only of dextral individuals, while some species are entirely sinistral, and some species are polymorphic for shell chirality, producing both dextrals and sinistrals in the same species. This particular genetic mechanism implies a lack of homozygous-dominant (R/R) individuals in the alternative shell phenotype, while the primary phenotype can have any of the genotypes of homozygous dominant, heterozygous (R/r), or homozygous recessive (r/r) in snails. In humans, the hair-whorl rotation, the direction in which the hair spins at the back of the head, is generally either clockwise or counterclockwise and has been associated with handedness, cerebral laterality, and sexual orientation. As such, direction of hair-whorl rotation is thought to be a phenotypic marker underlying the genetics of various behavioral phenotypes in our species. Previous research has already associated handedness with sexual orientation, psychosis, and autism spectrum disorders (ASD), but to the best of my knowledge, hair-whorl rotation has not been tabulated in autistic individuals. A recent theory has proposed that maternal-effect genes are involved in determining handedness and hair-whorl rotation in humans, in addition to various behavioral phenotypes in our species. These genes (possibly *RHD* and *RHCE*) predict a lack of homozygous-dominant individuals among the alternative phenotypes in humans, analogous to shell chirality in snails. If maternal-effect genes are interacting with biparentally-expressed genes to cause some cases of ASD and other behavioral

phenotypes in humans, then current genomic search results (i.e., linkage mapping using single nucleotide polymorphisms) for all of these genes will be obscured. To increase precision of genome searches during sibling studies, researchers should search for maternal-effect genes (i.e., never or almost never homozygous in the alternative phenotype; alleles shared *less* commonly than expected by chance in sets of affected siblings) in addition to biparentally-expressed genes (i.e., genes always or almost always homozygous in the alternative phenotype; alleles shared *more* commonly than expected by chance in siblings). If it can be shown that the snail chirality gene is homologous to the human handedness and hair-whorl genes, even if these genes turn out not to be *RH* genes, snails may still provide an animal model for evaluating possible environmental causes of ASD in humans. For example, aquatic snails, many of which have a short generation time and breed easily in captivity, could be treated with mercury to test the expression of the opposite chirality in their offspring. Other chemical agents or mixtures could also be tested in snails to determine possible correlates to environmental exposure in humans.

Introduction

A maternal-effect gene is defined as one in which the mother's genotype determines the phenotype displayed by her offspring. The best known and most studied example of such genes comes from Gastropods, or snails, but similar genes are also known to exist in other species (Beeman and Friesen 1999). Snails are hermaphroditic, so each snail possesses both male and female sex organs and thus each individual can serve either as mother (the individual that produces the eggs) or father (the individual that fertilizes the eggs). Snail shells are either right handed (dextral, clockwise spiral from apex of shell) or left handed (sinistral, counterclockwise spiral from apex of shell) in their development, and it is the unknown gene that determines handedness or chirality in snails that functions as a maternal-effect gene (Schilthuizen and Davison 2005). Most snail species consist only of dextral individuals, but some species are entirely sinistral, and some species are polymorphic for shell chirality, producing both dextrals and sinistrals within the same species (analogous to humans producing individuals who are either right handed or non-right handed).

The manner in which this genetic mechanism functions in snails is that the mother snail deposits a substance into each of her eggs that determines the chirality of the snails that develop from those eggs. This substance has never been identified, but it is known to exist because of the results from experimental studies. This unknown substance's composition depends on the mother's genes, however, not the offspring's, yet it somehow guides the development of asymmetry (and ultimately, chirality) in her offspring. If a snail species is all or mostly dextral, then dextral is defined as the primary phenotype for that species. If some individuals of that species are also sinistral, then this is defined as the alternative phenotype for that species. Similarly, in humans, the primary phenotype is defined as right handed because this phenotype is more common and the alternative phenotype is then defined as non-right handed. One can also extend the definition of primary phenotype in humans by defining the primary phenotype as right handed, left brained (i.e., cerebral laterality, the primary phenotype has left-sided language lateralization), clockwise hair whorl, heterosexual, non-psychotic, non-speech-dyslexic, and non-autistic. Thus, the primary phenotype is more

common among individuals of our species and the alternative phenotypes are much less so. These phenotypes will be discussed in more detail below, under the human model.

If a dextral snail is either homozygous dominant (R/R) or heterozygous (R/r) for the chirality gene, as discussed above, she produces and deposits a substance into her eggs that causes them to develop into individuals whose shells spiral dextrally. If she is homozygous recessive (r/r), however, then her eggs will become all or mostly sinistral individuals (Freeman and Lundehus 1982). Thus it is the mother's genes that determine the direction in which her offspring's shells coil, not their own genes. The reason it is important for snails to regulate the chirality of their shells is because many species, particularly those with a high spire, have difficulty mating with individuals of the opposite chirality (Schilthuizen and Davison 2005). Presumably some population genetic reason, such as greater fitness in individuals with the specified chirality, explains why the mother snail is causing her offspring to have similar chirality among themselves via her unknown, maternal-effect genes.

One prediction from this model is that the alternative phenotype will never be homozygous dominant. The primary phenotype can be homozygous dominant, heterozygous, or homozygous recessive, but the alternative phenotype can only be heterozygous or homozygous recessive. Thus, the alternative phenotype is never homozygous dominant, at least in the genetic etiologies, and this is a prediction that can be used in searching or testing for potential candidate genes.

Human Model

Recently, I proposed a similar maternal-effect genetic model for handedness in humans, with some important differences, as discussed in Hatfield (2006). Regardless of the differences, this model leads to the same prediction in humans as in snails (i.e., a lack of homozygous-dominant individuals among the alternative phenotypes). It should be noted that any such gene that operates this way would probably lead to this same prediction. However, it is an unusual and, therefore, interesting prediction. It is also testable.

Klar (2003) proposed a model for the gene that determines handedness and hair-whorl rotation in humans. According to this model, humans are either right handed or non-right handed, while hair-whorl rotation (i.e., the direction the scalp hair turns at the back of the head) can be either clockwise, counterclockwise, or in rare cases, even more complicated. Most people (> 95%) have a single, dominant hair whorl, either clockwise or counterclockwise, but some people have double hair whorls, with both clockwise and counterclockwise hair whorls on the same scalp (Wunderlich and Heerema 1975), and other rare patterns also exist (R. Lippa, personal communication). Klar (2003) proposed that a common genetic mechanism controls both handedness and hair-whorl rotation in humans (with this result being replicated by Beaton and Mellor 2007), that this gene was possibly also related to cerebral laterality (with evidence provided later by Weber et al. 2006), and may also be involved in speech dyslexia (e.g., stuttering) in some individuals. He further proposed that this unknown, *RGHT* gene determines (or at least is somehow involved in determining) the various phenotypes for these traits in our species. Klar (2004a) speculated that this same gene may be implicated in the etiology of some forms of mental illness

(specifically, bipolar disorder and schizophrenia) and Klar (2004b) inferred that this putative gene is associated with sexual orientation in humans by demonstrating an empirical association between hair-whorl patterns and male sexual orientation. Considerable earlier research demonstrated a similar association between handedness and sexual orientation, with homosexual individuals displaying higher rates of non-right handedness than heterosexual individuals (Lalumière et al. 2000, Lippa 2003).

It is informative to describe in more detail the mechanism that Klar (2003) has proposed for how the *RGHT* gene leads to asymmetries in the development our species and others. Specifically, his model provides a mechanism for differentiation of particular cell types during mitosis (Klar 2004b, Armakolas and Klar 2006, 2007). Klar believes that the *RGHT* gene acts to cause non-random segregation of DNA strands on chromosome 11 during mitosis in our species, and this leads to differentiation of certain cell lines in the developing embryo, which ultimately leads to asymmetrical placement of brain structures in humans. Because of the non-random segregation of DNA strands during mitosis, some cells receive different genetic information relative to other cells. Thus, this epigenetic mechanism allows for the on-off switches of the genes to be different between the daughter cells due to the non-random segregation of the DNA chains during mitosis, ultimately leading to differentiation into certain cell types. Klar's proposed mechanism is unorthodox and surprising, however, as it contradicts the conventional assumption that DNA strands are allocated randomly to daughter cells during mitosis.

Klar's genetic model operates as follows. If an individual is homozygous recessive (r/r) for the *RGHT* gene, he or she develops handedness and hair-whorl rotation at random during fetal development. Thus, 50% of these individuals will be right handed, and 50% will be non-right handed, and independently, 50% will have clockwise hair whorl, and 50% will have counterclockwise hair whorl. Klar termed this process the *random recessive* pattern of brain development. If an individual is homozygous dominant (R/R) or heterozygous (R/r), then these individuals develop clockwise hair whorl and become right handed according to Klar's model. Klar does not have an explanation for more complicated hair whorls, however, and excluded such individuals from his research.

My theory (Hatfield 2006) is an extension of Klar's model in which I proposed maternal-effect genes (possibly *RHD* and *RHCE*) determine handedness and hair-whorl rotation and are also involved in sexual orientation and other behavioral phenotypes in humans, with maternal immunization being the mechanism for how the maternal effect is realized. Interestingly, *RHD* was recently linked to sexual orientation in humans (Ellis et al. 2008). In snails, the mother determines the chirality of her offspring, so the father's genes are not important for determining chirality in snails. In humans, however, assuming my model is correct, the father's genes do sometimes have an effect, depending on whether the mother maternally immunizes or not. Thus, first-born children, for example, would tend to have their handedness and hair-whorl rotation determined by both the father's and the mother's genes following Klar's model, but as the mother bears more children, and if she maternally immunizes before or during the later pregnancies, then her genes are more important for determining the phenotypes of these later-born children according to my model.

Thus, first-born children may follow Klar's model fairly closely, but later-born children deviate from this model more and more, as maternal immunization becomes stronger. This is

the maternal effect. Some mothers may not maternally immunize at all, so these families would also follow Klar's model. My extension of Klar's model basically implies that some heterozygous individuals also go through the random-recessive pattern of choosing handedness and hair-whorl rotation at random, due to maternal immunization by their mothers. More complicated models are also possible.

In Hatfield (2006), I proposed that autism spectrum disorders (ASD) in humans may be associated with our maternally-immunizing genes (specifically *RHD* and *RHCE*, with a related hypothesis being that *RHD* is the *RGHT* gene). Asbury (2006) also proposed that the *RGHT* gene may be associated with ASD. Indeed, handedness has been shown to be associated with ASD (Bryson 1990), as well as with sexual orientation (Lippa 2003) and psychosis (Klar 2003). The fact that more males than females display all of these alternative phenotypes (except bipolar disorder, apparently) provides some evidence for maternal immunization as well, although certainly other explanations are possible, such as the effects of a sex-linked gene and prenatal variations in exposure to sex hormones. Evidence for the maternal-immunization hypothesis comes from studies of the fraternal birth-order effect found in homosexual males (i.e., the consistently demonstrated phenomenon that each additional older brother increases a man's odds of being homosexual; Blanchard 2004, as discussed in Hatfield 2006) and a similar birth order effect found with handedness in chimpanzees (Hopkins et al. 2005, discussed by Wolman 2005). These findings, coupled with evidence from the human monozygotic twin-concordance studies, may help suggest possible biological models.

Of course, a model is of limited value unless data are eventually collected to test the model and estimate its parameters, but existing results suggest *a priori* that certain models may be more appropriate than others, if maternally-immunizing genes are involved as maternal-effect genes in humans. An interaction of three maternal-effect genes (acting the way *RHD* does, in which male fetuses are more likely to initiate maternal immunization than female fetuses; see Blanchard 2004) working as Klar (2003) and Hatfield (2006) proposed, would lead to many more males than females displaying the alternative phenotype (ASD, in this case) and it could lead to a twin-concordance prediction of 7/8 or 87.5%, if all of the seven possible alternative phenotypes are more susceptible to ASD and the primary phenotype (i.e., right handed and left brained) is not susceptible. This value of 87.5% is within the range 60-95% given in the literature recently (Schellenberg et al. 2006) for monozygotic twin concordance for ASD, but certainly other models are possible. Just one maternal-effect gene or two interacting maternal-effect genes can lead to a twin-concordance prediction of 50%, as is found in the literature on sexual orientation (Lalumière et al. 2000), but depending on the model, can also yield twin-concordance predictions of 25% or 75%.

If maternal-effect genes are involved in producing the alternative phenotypes discussed above, then they are likely not the only genes involved. Indeed, even a maternally-suppressed paternally-associated gene (*LRRTM1*) was recently found to be involved in handedness and schizophrenia in humans via an epigenetic mechanism (Francks et al. 2007). Other studies of schizophrenia have implicated a number of contributing genes (e.g., see Law et al. 2006, Barnett et al. 2007, Bellon 2007), in addition to *RHD* (Palmer et al. 2002), and similar studies have been conducted for ASD (e.g., see Ylisaukko-oja et al. 2005, Campbell et al. 2006). In genetic terms, then, there may be several (or many) different etiologies leading to the same

phenotype, or alternatively, there may be an interaction among maternal-effect genes and biparentally-expressed genes (i.e., autosomal, non-maternal-effect genes) to cause the development of such phenotypes. It is certainly possible that there are some (or many) environmental causes for the development of these phenotypes as well, as discussed in Hatfield (2006), and it is also possible that genetic factors interact with environmental triggers or factors. Regardless, any compound or chemical agent that interferes with the function of the *RGHT* gene in a developing fetus may be responsible for some cases of ASD.

Genome Searches

One powerful way to search for genes associated with particular traits is to do linkage mapping using single nucleotide polymorphisms (SNPs) from data generated with sibling studies. In such studies, one finds a sample of families that have two or more siblings displaying the phenotype of interest (e.g., ASD, bipolar disorder, homosexuality, schizophrenia, etc.) and search the siblings' genomes for SNPs in which alleles are *more* commonly shared among the siblings than expected by chance in such siblings. Such searches have been fruitful in finding genes in many instances, but for the various alternative phenotypes discussed in this chapter, such searches have not been extremely successful to date (IMGSAC 2001, Levinson et al. 2002, Mustanski et al. 2005, Schellenberg et al. 2006, Suarez et al. 2006, Crow 2007, Baum et al. 2008). These searches look for genes in which the alternative phenotypes are always or almost always homozygous recessive (or dominant). It makes sense to look at this tail of the statistical distribution of such genes (i.e., the right-hand tail), because this is indeed how many biparentally-expressed genes function. However, maternal-effect genes, like those found in snails and proposed in humans, do not fit this model. In fact, it is the opposite tail (ironically, the left-hand tail) of the statistical distribution of such genes that may help locate maternal-effect genes, because this type of maternal-effect gene is never or almost never homozygous dominant in the alternative phenotype. Thus, to find these genes, one will need to search for SNPs in which alleles are *less* commonly shared among the sets of affected siblings than expected by chance in such siblings. Existing SNP data could certainly be re-analyzed to search for such maternal-effect genes.

If the genetic etiologies for these phenotypes include interactions between biparentally-expressed genes and maternal-effect genes (and paternal-effect genes?) these interactions may be difficult to detect with linkage mapping, especially if many different genes or genetic mechanisms are involved. However, it may be possible to detect such a signature with large sample sizes, if one factors into the algorithm that there is an interaction between maternal-effect and biparentally-expressed genes. If environmental pathways are also involved in the development of some or all of the alternative phenotypes, this further complicates the search for relevant genes.

Conclusion

The ideas presented in this chapter and Hatfield (2006) provide the motivation for testing hypotheses concerning whether maternal-effect genes are involved in ASD and other alternative phenotypes in humans. The similarities between the snail chirality gene and the proposed human handedness and hair-whorl genes may just be an analogy, but if true, it is possible that they are homologous as well, not just analogous. Thus, it would be useful to identify the snail chirality gene, as well as the human genes, to determine if they are similar. One hypothesis is that these maternal-effect genes are all *RH* genes (in particular, *RHD* and *RHCE*, in humans). Of course, it is also possible that none of these genes are *RH* genes, but if one finds the snail chirality gene, then one may be able to find the human handedness and hair-whorl genes as well, if they are similar (i.e., homologous) to the snail chirality gene. If all of these genes are eventually demonstrated to be homologous (*RH* genes or otherwise) then snails may provide an animal model for studying the production of the alternative phenotypes in humans (e.g., ASD). Freshwater snails of the genus *Lymnaea* are already used in toxicity studies (Nazrul Islam et al. 2001, Pyatt et al. 2003), and some of these same species of *Lymnaea* are also polymorphic for shell chirality (Schilthuizen and Davison 2005). Retrospective studies of exposure in humans are certainly possible and should be conducted (i.e., estimate exposure of pregnant mothers to some chemical agent of interest and correlate such exposure with, say, ASD rates in various areas). However, even if the retrospective studies are conducted and they suggest a correlation with some chemical agent, one can never do the definitive experimental studies in humans in which one exposes pregnant mothers to hypothesized environmental triggers (mercury, for example) to determine if exposure causes some of their children to display ASD. Thus, it is impossible to prove causation with such retrospective studies, only correlation. However, one can expose snails to mercury to determine if such exposure causes some of their offspring's shells to coil in the opposite direction. Thus, if the snail chirality genes and human handedness and hair-whorl genes are eventually proven to be homologous, snails could be used to test various chemical agents or mixtures to assess their effects on chirality. Snails would then constitute a useful animal model for studying the production of the alternative phenotypes in humans, at least regarding the function (or disrupted function) of the chirality genes.

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