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The genetic basis of hair whorl, handedness, and other phenotypes

Jeff S. Hatfield *

USGS Patuxent Wildlife Research Center, 12100 Beech Forest Road, Laurel, MD 20708, USA

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Summary Evidence is presented that *RHD*, *RHCE*, and other *RH* genes, may be interesting candidates to consider when searching for the genetic basis of hair whorl rotation (i.e., clockwise or counterclockwise), handedness (i.e., right handed, left handed or ambidextrous), speech laterality (i.e., right brained or left brained), speech dyslexia (e.g., stuttering), sexual orientation (i.e., heterosexual, homosexual, bisexual, or transsexual), schizophrenia, bipolar disorder, and autism spectrum disorder. Such evidence involves the need for a genetic model that includes maternal immunization to explain some of the empirical results reported in the literature. The complex polymorphisms present among the maternally immunizing *RH* genes can then be used to explain other empirical results. Easily tested hypotheses are suggested, based upon genotypic (but not phenotypic) frequencies of the *RH* genes. In particular, homozygous dominant individuals are expected to be less common or lacking entirely among the alternative phenotypes. If it is proven that *RH* genes are involved in brain architecture, it will have a profound effect upon our understanding of the development and organization of the asymmetrical vertebrate brain and may eventually lead to a better understanding of the developmental processes which occur to produce the various alternative phenotypes discussed here. In addition, if *RH* genes are shown to be involved in the production of these phenotypes, then the evolutionary studies can be performed to demonstrate the beneficial effect of the recessive alleles of *RHD* and *RHCE*, and why human evolution appears to be selecting for the recessive alleles even though an increase in the frequency of such alleles may imply lower average fecundity among some individuals possessing them.
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Introduction

Amar Klar realized there could not be a gene controlling the spiral of scales on a pinecone when he noticed that 50% of pinecones have scales that spin clockwise (C) and 50% spin counterclockwise (CC) in their arrangement around the pinecone [1]. He then realized there must indeed be a gene controlling how human scalp hair spins at the back of the head, because 92% of the population he sampled in suburban Maryland had C hair whorl while only 8% had CC [2]. If genes were not involved, Klar reasoned, humans would display 50% C and 50% CC hair whorl, like the scales on pinecones. Klar has since argued that this hair whorl gene (which he calls *RGHT*) determines handedness in humans [2] and is also involved in sexual orientation [3], schizophrenia and bipolar disorder [4]. Klar [2–4] also believes this gene controls speech laterality

* Tel.: +1 301 497 5633; fax: +1 301 497 5545.
E-mail address: jhatfield@usgs.gov.

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(i.e., cerebral laterality, whether language processing is located on the left side or the right side of the brain), and may be involved in speech dyslexia (e.g., stuttering). I contend that some cases of autism spectrum disorder may be linked to this gene as well.

As farfetched as all of this may sound, the various alternative phenotypes associated with the traits discussed above do have some things in common: each is relatively rare (usually around 10% or less in the population, but <1% for schizophrenia, bipolar disorder, and autism), each is more common in males than females (except for bipolar disorder), and, if one member of a monozygotic twin displays one of the alternative traits (e.g., left handed or ambidextrous), then the other twin has about a 50% chance of having the trait [2—7]. Furthermore, various studies also have discussed associations among some of these phenotypic traits, such as non-right handedness and speech laterality [2], non-right handedness and psychosis [2,4], non-right handedness and autism [8], autism, schizophrenia and bipolar disorder [9], non-right handedness and sexual orientation [5,10], and speech laterality and sexual orientation [11]. Another interesting commonality is that when researchers look for the gene or genes responsible for these alternative behavioral phenotypes, they often find candidate genes, but they never seem to find much of significance, even though genetic mechanisms are thought to be involved in all of them [12—14].

Klar [2] developed a model, which he calls the *random recessive* model, to explain some of the patterns among his sample of left-handed and ambidextrous people. He estimates that the *RGHT* gene has frequencies of 60% dominant (*R*) and 40% recessive (*r*) in the population he measured in Maryland, leading to 84% of individuals being homozygous dominant (*R*/*R*) or heterozygous (*R*/*r*), and 16% being homozygous recessive (*r*/*r*). If a fetus carries the dominant form of the gene, Klar [3] believes he or she will become right handed, left brained, heterosexual (later in life), and have C hair whorl (i.e., the primary phenotype). Klar hypothesizes that a homozygous recessive fetus, however, goes through a *random recessive* pattern of brain development. Thus, 50% of such fetuses will become right handed and 50% will become left handed or ambidextrous. Independently, 50% will be right brained and 50% will be left brained in how they process speech, and independently again, 50% will have C hair whorl and 50% will have CC hair whorl. The Natio- nal Institute of Health is currently conducting a clinical trial [15] searching for the *RGHT* gene, so we may know more about this soon.

The Rh hypothesis

I would like to suggest a candidate gene for *RGHT*, one of the genes of the Rh system, *RHD*. *RHD* has the required frequencies in the US, of which 85% of the population is Rh+ and 15% is Rh— [16]. Previous research has already associated *RHD* with non-right handedness [17,18], schizophrenia [19], autism [20],[1] and speech disorders [21].

There is also an association between *RHD* and handedness at the population level (Fig. 1), with the percentage of right-handed individuals [22] being approximately equal to the percentage of Rh+ individuals [23] in each population for which I have found statistics. Oddly enough, the correlation does not show up at the individual level. A data set [24] containing information concerning handedness and Rh phenotype collected on women (n = 1783) in the US Air Force in 1968 showed only a slightly decreased incidence of right handedness in Rh— women compared to Rh+ women and the difference was not significant (89% right handedness in Rh+ women vs. 87% right handedness in Rh— women, P = 0.18, one-sided Fisher's exact test). An explanation for this negative result will be discussed below.

Maternal immunization

Researchers [5,25] have hypothesized that *maternal immunization* (MI) may be one component of how sexual orientation is determined in humans. *RHD*, and to a lesser extent the other *RH* genes, exhibit MI [26]. *RHD* has long been known to sometimes cause a serious, often fatal condition called hemolytic disease of the newborn (HDN) when an Rh— mother produces antibodies to an Rh+ fetus she is carrying [16,26]. It is hypothesized [5,25] that the ''gay'' gene, if it exists, might display MI because homosexual men are significantly more likely to have an older brother than the general population, suggesting that production of maternal antibodies to the gay gene of an older sibling might somehow make younger brothers more likely to become homosexual, bisexual, or transsexual (i.e., non-heterosexual) although other explanations also exist, as discussed by Ray Blanchard [25].

Interestingly, Blanchard [25] cites numerous studies showing that MI is more commonly initiated

[1] Interestingly, this study [20] finds autistic individuals to be significantly less likely to have an *RHD* incompatible mother than control families, suggesting that perhaps another of the *RH* genes is involved. *RHCE* is closely linked to *RHD* on chromosome 1, possibly also involved in brain architecture, and *RHCE* is also highly polymorphic in humans.

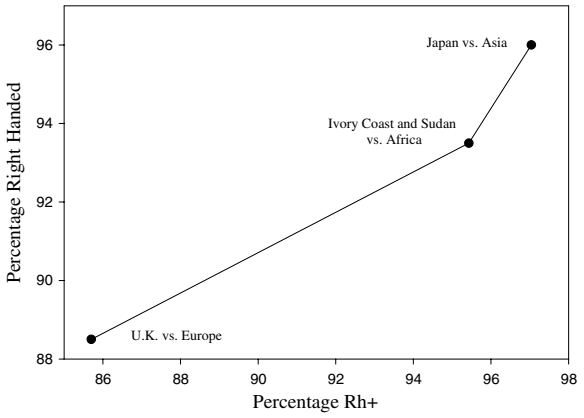

Figure 1 Percentage of right handedness [22] vs. Rh+ phenotype [23] for various human populations.

by male than female fetuses in the case of *RHD*, something that would lead to more males displaying the alternative behavioral phenotypes, if *RGHT* is found to be *RHD*. The effect of MI on the creation of non-heterosexuals is not insignificant, however, especially for males, as it is estimated that 28.6% of male homosexuals (95% CL: 14.8%, 48.0%) can attribute their sexual orientation to such a mechanism [27]. Oddly, although it is hypothesized that both MI and genes are involved in determining sexual orientation as two separate mechanisms [25,27], with genes determining sexual orientation of first born children, and MI being involved in later born children, the *RH* genes have never been investigated for their involvement in sexual orientation. The *RH* genes have the unique ability to explain how sexual orientation is determined, both for first born children, and for children of higher birth order.

Suppose for the argument below that the *RGHT* gene is indeed *RHD*. We know that *RHD* exhibits MI, and we suspect the presence of the *RGHT* protein or gene product causes a developing fetus to have C hair whorl and become right handed and left brained. Thus, Rh− fetuses would go through the random recessive pattern of brain development discussed above, and Rh+ fetuses carried by Rh+ mothers would display the primary phenotype (i.e., right handed, left brained, C hair whorl). However, Rh− mothers carrying Rh+ fetuses, due to the maternal−fetal antibody reaction, may cause some of their Rh+ fetuses (especially male fetuses of higher birth order) to enter the random recessive pathway of brain development, even though these fetuses carry the dominant form of the gene. Note that these children must be heterozygous, because they are Rh+ with an Rh− mother. Thus, before treatment of *RHD* maternal−fetal genotype incompatibility became widespread, there would have been an increase in heterozygous individuals displaying the alternative phenotypes, due to the maternal−fetal genotype incompatibility, and concurrently, a decrease in (or perhaps a total lack of) homozygous dominant individuals among the alternative phenotypes. Looking only at phenotypic expression (ins-tead of the genotypes), one would not see much of a difference in the percentages of the Rh+ phenotype between classes of the primary phenotype (e.g., right handed) and the alternative phenotype (e.g., non-right handed). This may be why the data set of Air Force women did not show a significant association between Rh status and handedness, because the association does not show up when looking only at phenotypic frequencies, and thus why nobody has ever found a relationship between handedness and *RHD* when studied at the individual level. If correct, the same may hold true for the other behaviors as well.

Why have previous genome scans not identified this gene?

If the *RGHT* gene is found to be one that exhibits MI, then even if it is not *RHD*, it will not show up in the usual genome scans performed to find such genes. *RHD* exhibits non-Mendelian inheritance and the mother's genotype (and also if she has had any transfusions or prior pregnancies) may be as important in determining the phenotypic expression of her offspring as her offspring's own genotypes are.

For example, a recent study [14] looked at homosexual brothers and found no strong candidate genes for this alternative phenotype, although there were some genes of lesser significance. If any of the genes for which these authors are searching exhibits MI, however, then the sets of homosexual brothers in this study will likely be a mixture of heterozygous and homozygous recessive individuals, even within the same family sometimes, and this will obscure the search for these genes in their study. This is because the authors were using a model to search for alleles that assumes the alleles will be more commonly shared among the sets of homosexual brothers than that expected by chance in such brothers. This model assumption is violated if the homosexual brothers are a mixture of heterozygous and homozygous recessive individuals, and therefore the algorithm will fail to find such genes. Similarly, although research [28] has found an association between chromosome 1 (on which *RHD* is located) and schizophrenia, a more recent multi-

center study [13] found no such association, although again, that later study's sample of siblings would not find such an association if the gene or genes for which they are looking exhibit MI and a portion of the alternative phenotypes are heterozygous, in addition to the homozygous recessives.

I should mention that I am not advocating that other genes or genetic mechanisms or even some environmental causes are not involved in some or all of these alternative behavioral phenotypes. Almost surely multiple mechanisms are at work here, and quite possibly, the previous genome scans [12–14] have identified relevant genes also involved in modifying the phenotypic expression of these various traits. For schizophrenia and bipolar disorder, for example, Klar [4] believes that the *RGHT* gene causes patterned chain segregation to occur on chromosome 11, which then may cause an individual to go on to exhibit schizophrenia or bipolar disorder later in life. Regardless, once the *RGHT* gene is found, it will undoubtedly lead to a much better understanding of the other genes or mechanisms that cause some individuals to display some of the behavioral phenotypes discussed here. If *RGHT* is found to be *RHD*, one also wonders what all of our other *RH* genes do. These genes are shared by humans and other species, some of these genes are also polymorphic like *RHD* is in humans, some of these genes cause MI as well, and all have unknown function, except that a total lack of all Rh antigens causes clotting abnormalities in the red blood cells of such individuals [26]. *RHD* is uniquely human though, having arisen from the *RHCE* gene by a tandem gene duplication event that occurred 5–12 million years ago in our ancestors [29]. Interestingly, that study [29] used a diffusion analysis to conclude that *RHD* and *RHCE* are probably under strong selection pressure, and so the unusual pattern of polymorphisms present in these genes is not likely due to random genetic drift as once thought. *RHCDE* gene frequencies are presented in Table 1 for various populations [23].

Additional hypotheses

If one is willing to use the imagination, some additional hypotheses come to mind. For example, there is obviously an association between handedness, speech laterality, and sexual orientation, if only because >90% of people are right handed and left brained, and >90% of people are heterosexual, and this has been mentioned by Klar [2,3]. Whether this correlation extends to the alternative behavioral phenotypes (e.g., non-heterosexuals) remains to be tested. However, using the statistics presented by Klar [2] and portrayed in Table 2, there are two very different brain architectures shown in Table 2 that account for about 8% of the population that Klar tabulated in Maryland: right-handed, right-brained individuals and non-right-handed, left-brained individuals. If, as Klar [3] hypothesizes, right-handed, left-brained people are heterosexual, one wonders if non-heterosexuals may be right handed and right brained or non-right handed and left brained. Note that I am not implying causation, only correlation, as other brain structures could actually be involved that determine the sexual orientation. Note also that I am not saying that all right-handed, right-brained individuals or non-right-handed, left-brained individuals are non-heterosexual, but only that all non-heterosexuals

Table 2 Approximate percentages (%) of handedness and speech laterality implied for a population that is 92% right handed, for which 96% of right-handed individuals are left brained, and for which 50% of non-right-handed individuals are right brained [2]

Handedness	Speech laterality	
	Right brained	Left brained
Right handed	4	88
Not right handed (left handed and ambidextrous)	4	4

Table 1 Genotypic frequencies (%) of *RHCDE* for the native populations of Africa, Asia, and Europe [23]

	Genotypic frequencies (%)							
	CDE	*CdE*	*CDe*	*Cde*	*cDE*	*cdE*	*cDe*	*cde*
Africa	~0	~0	11.71	1.30	6.73	~0	60.34	19.49
Asia	1.02	~0	61.36	1.82	14.12	0.66	6.00	14.98
Europe	0.49	~0	45.02	1.73	13.28	~0	3.37	35.43

Capital letters denote dominant alleles, lower case letters denote recessive alleles, but note that the recessive allele (*d*) for *RHD* actually implies the absence of any *RHD* antigen.

may have one of these two brain architectures. This hypothesis is not inconsistent with empirical data which show that homosexuals are more likely to be non-right handed [5,10] and more likely to be right brained [11] than the general population. This hypothesis could easily be tested using *f*MRI to determine speech laterality on a sample of homosexuals whose handedness preference has been determined using the handedness test discussed by Klar [2].

There is another interesting hypothesis that comes to mind. Klar [3] hypothesizes that the dominant allele of the *RGHT* gene causes fetuses to become right handed and left brained, but when homozygous recessive, somehow these two structures become uncoupled in their asymmetrical placement during fetal brain development and these fetuses then go through the random recessive pattern of brain formation. How these brain structures become uncoupled is not discussed by Klar. Suppose, however, that *RHD* determines handedness, and *RHC* determines the dominant hair whorl and speech laterality. Other hypotheses are certainly possible, but this is one hypothesis that I will explore below, to illustrate calculation of expected values from *RH* polymorphisms.

Using the gene frequencies from Table 1 for native Europeans, for example, one can calculate some interesting expected genotypic and phenotypic frequencies for this population (Table 3). Using the model discussed above in which non-heterosexuals are assumed to be right handed and right brained or non-right handed and left brained, assuming *RHD* determines handedness and *RHC* determines dominant hair whorl and speech laterality, and assuming a random recessive pattern of brain development for each of *RHD* and *RHC* when in the recessive state, one can estimate that 3.77% of the native population of Europe is expected to be non-right handed and left brained, 10.42% is expected to be right handed and right brained, no more than 14.19% is expected to be non-heterosexual, and 36.73% of the non-heterosexual Europeans are expected to have CC hair whorl (Table 3). Thus, under this model, about 27% of non-heterosexual people of European ancestry are expected to be non-right handed, and about 37% of non-heterosexuals of European ancestry are expected to have CC hair whorl. These expected values are not far from the estimates for the percentage of non-right handedness in homosexuals [5] and the percentage of CC hair whorl in non-heterosexuals [3], although the populations sampled in those studies may not have exactly the same *RH* gene frequencies as native Europeans [23]. Klar's empirical estimate of 29.8% CC hair whorl was

Table 3 Genotypic frequencies (%) of *RHCDE* for the native population of Europe [23]

			Father (%)							
	Haploid %		*CDE*	*CdE*	*CDe*	*Cde*	*cDE*	*cdE*	*cDe*	*cde*
			0.49	∼0	45.02	1.73	13.28	∼0	3.37	35.43
Mother (%)	*CDE*	0.49	∼0	∼0	0.22	0.01	0.07	∼0	0.02	0.17
	CdE	∼0	∼0[a]	∼**0**	∼0[a]	∼**0**	∼0[a]	∼**0**	∼0[a]	∼**0**
	CDe	45.02	0.22	∼0	20.27	0.78	5.98	∼0	1.52	15.95
	Cde	1.73	0.01[a]	∼**0**	0.78[a]	**0.03**	0.23[a]	∼**0**	0.06[a]	**0.61**
	cDE	13.28	0.07[a]	∼0[a]	5.98[a]	0.23[a]	*1.76*	∼*0*	*0.45*	*4.71*
	cdE	∼0	∼0[a]	∼**0**[a]	∼0[a]	∼**0**[a]	∼*0*[a]	∼**0**	∼*0*[a]	∼**0**
	cDe	3.37	0.02[a]	∼0[a]	1.52[a]	0.06[a]	*0.45*	∼*0*	*0.11*	*1.19*
	cde	35.43	0.17[a]	∼**0**[a]	15.95[a]	**0.61**[a]	*4.71*[a]	∼**0**	*1.19*[a]	***12.55***

Haploid frequencies (%) are shown in the 3rd row from the top and the 3rd column from the left. Expected diploid frequencies (%), assuming random mating, are shown in the body of the table. Ignoring the effects of maternal immunization,[a] and assuming the model discussed in the text in which *RHD* determines handedness and *RHC* determines hair whorl and speech laterality, the bolded percentages are those that will produce non-right-handed left-brained individuals (expected to be 50% of each bolded number, except for the cell in the lower right, which has a 25% expected value) and the italicized percentages are those that will produce right-handed right-brained individuals (expected to be 50% of each italicized number, except for the cell in the lower right, which has a 25% expected value)[b].

[a] These cells are expected to have slightly increased numbers of random recessive alternative phenotypes due to the effects of maternal immunization on heterozygous offspring with higher birth order, especially male offspring, but the magnitude of this effect is unknown. It is not insignificant, however [27].

[b] Under this model, and making the assumptions discussed in the text, 3.77% of the native population of Europe is expected to be non-right handed and left brained (from bolded numbers), 10.42% is expected to be right handed and right brained (from *italicized* numbers), no more than 14.19% is expected to be non-heterosexual, and 36.73% of the non-heterosexuals are expected to have counterclockwise (CC) hair whorl.

estimated from a sample of $n = 272$ mostly non-heterosexual men in Delaware [3].

Another interesting result can also be explained by this model. Recently, it was shown that there is a positive association between birth order and the production of right-handed male homosexuals [30]. This is exactly what would be expected to happen with the model discussed above due to MI of *RHC*, especially given that treatment of *RHD* (but not *RHC*) maternal—fetal genotype incompatibility has become widespread since it began in the 1960s [31]. Of course, it is entirely possible that other models or genes would be more appropriate for explaining some of these various empirical results, but I hope I have generated some interest in exploring *RHCDE* to help explain some of these results. More complicated models are also possible, such as an interaction between *RHD* and *RHCE*, and perhaps other *RH* genes, but this cannot be determined until empirical data on *RH* genotypic frequencies are compared among the primary and alternative phenotypes. Another possibility is that *RHD* actually determines the speech laterality and *RHC* determines handedness, and perhaps *RHE* is involved somehow, but again, it will only be possible to distinguish among the various competing models once empirical data on genotypic frequencies become available.

Furthermore, any environmental contaminant that is found to interfere with the function of the *RGHT* gene product or protein in the early stages of a developing fetus would also be of great interest to the scientific community. For example, other causes of left handedness are also hypothesized, such as brain injury [32], although such causes are expected to be much less frequent than a genetic basis [33]. However, such phenomena could allow for some homozygous dominants to go through the random recessive pattern of brain development, but if it occurs much less frequently than the genetic mechanism, then there still should be significantly fewer homozygous dominants found among the alternative phenotypes when compared to the primary phenotype.

Conclusion

The incidence of CC hair whorl needs to be precisely estimated for groups having the various behavioral phenotypes discussed above and for various populations of people as well. Of course, I would especially like to see the *RH* genotypic frequencies of mothers and offspring compared among various groups of the offspring, such as individuals with C hair whorl vs. individuals with CC hair whorl, or right handers vs. left handers, or heterosexuals vs. homosexuals, because this would provide an elegant test of the Rh hypothesis since significantly fewer homozygous dominants are expected among individuals displaying the alternative phenotypes. One can envision such a study being conducted for each of the alternative phenotypes, in order to determine which of the *RH* genes are involved in the production of each phenotype. Any of the researchers [17—21] who have already shown an association between *RHD* maternal—fetal genotype incompatibility and one of the alternative phenotypes may already have such data. In particular, one study [19] may have this data because these researchers actually determined *RHD* genotypes for a sample of schizophrenic patients. Hopefully, the required genotypic data to do these tests will be collected, or become available from the previous studies, at some point soon.

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