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Breast cancer predisposition and brain hemispheric laterality specification likely share a common genetic cause

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Abstract

The majority of breast cancer cases seen in women remain unexplained by simple Mendelian genetics. It is generally hypothesized that such non-familial, so-called sporadic cases, result from exposure of the affected individuals to a cancer-causing environment and/or from stochastic cell biological errors. Clearly, adverse environment exposure can cause disease, but is that necessarily the cause of most sporadic cases? Curiously, female breast cancer patients who were selected to prefer right-hand-use reportedly exhibited a higher incidence of reversed-brain hemispheric laterality when compared to that of the public at large. Notably, such a higher level of hemispheric reversal is also found in healthy, left-handed or ambidextrous persons. Based on the association between these disparate traits, a new hypothesis for the etiology of sporadic breast cancer cases is advanced here; breast cancer predisposition and brain laterality development likely share a common genetic cause.

1. The etiology of sporadic breast cancer cases in women is unknown

Breast cancer is the most frequent cancer in women, with nearly one million new cases reported every year around the world [1]. Only about 5% of all breast cancer cases are due to the segregation of germ-line mutations in specific families. Two major genes, *BRCA1* [2] and *BRCA2* [3], account for about 20% of familial cases. Furthermore, mutations in other high-susceptibility genes account for only 5% of cases. Thus, a majority of breast cancer cases are sporadic.

Despite extensive research conducted over many years, the reason behind sporadic cases of breast cancer remains unknown. Many genome-wide linkage analyses of non-*BRCA1/2* families have identified multiple single nucleotide polymorphisms that are suggested to be linked to putative cancer-susceptibility genes, but such findings have failed replication in subsequent studies. Thus, linkage analyses have not yet convincingly identified cancer-susceptibility genes [4,5]. This question, which carries important interdisciplinary significance for human health-related research, is addressed here by advancing a new explanation for the results of a previous study that recorded a remarkable correlation between brain hemispheric laterality development and sporadic breast cancer cases in women [6].

2. The brain laterality and hand-use preference traits are associated in complex ways

The left and right hemispheres of the human brain perform different cognitive functions. This hemispheric lateralization is associated with right-versus-left-hand use preference (i.e., handedness) for one-handed tasks, such as writing, throwing a ball, holding a tennis racket, in yet unexplained and fascinating ways. About 97% of right-handed(RH) persons develop speech, language processing, and logic in the left hemisphere, the so-called “dominant hemisphere,” and their “automatic hemisphere,” on the right side, processes emotional information of intuition, feelings, art, and creativity. In contrast, the dominant hemisphere is located on the right side in 40% to 50% of left-handed and ambidextrous individuals (reviewed in [7]). Usually, for simplicity, the left-handed and ambidextrous individuals are collectively referred to as non-right-handed (NRH) persons. Thus far, the biology of brain laterality development and this complex association with hand preference have remained undefined. Hemispheric lateralization anomalies are proposed to have important consequences for developing psychiatric disorders. Thus, defining the biological basis of this complex association is important for human health [7].

The hemispheric functional specialization is also associated with structural asymmetries. The occipital pole is frequently wider in the left hemisphere than in the right, and the right frontal area is often wider than the left frontal area in RH persons. The overall functional and structural asymmetry of NRH persons is much more variable, nearly randomly distributed with respect to the left-versus-right hemisphere, compared to the much more biased arrangement found in the majority of RH persons [7].

3. The high association of reversed brain hemispheric laterality was discovered in breast cancer patients

Sandson et al. [6] tested the previously proposed hypothesis [8] that an altered intrauterine hormone environment causes anomalous brain laterality development of the fetus, and secondly, that such exposure predisposes the fetus to subsequently develop breast cancer anytime in adulthood. They analyzed data from breast cancer and healthy subjects whose brain cranial computed tomography had been recorded previously to measure brain laterality. Both groups of subjects consisted of white, RH women, either consecutive breast cancer cases or consecutive healthy individuals who visited the Dana-Farber Cancer Institute, Boston, Massachusetts, USA. The study reported lower prevalence of reversed brain asymmetry in the control subjects, as had been reported in previous studies. However, the breast cancer subjects exhibited remarkably increased ($p < 0.0001$) prevalence of reversed asymmetry when compared with controls (Table 1; 49% in cancer patients versus 18% in control subjects). To avoid the confounding effect of brain metastasis on brain laterality measurements, patients with brain metastasis were not included in the study. The authors concluded that brain laterality measurements provide indirect support for the hormone hypothesis for the etiology of breast cancer.

4. A new hypothesis: Breast cancer and brain laterality traits are conferred by the same genetic etiology

Another explanation for breast cancer etiology is advanced here. This explanation is based on research conducted on brain laterality and handedness etiology. The random brain asymmetry of cancer patients matches remarkably well with that exhibited by healthy NRH persons at large as discussed above [7]. Therefore, an alternative interpretation for the results advanced here is that the genetic factor(s) that confers near-random brain laterality distribution independently predisposes individuals to develop breast cancer anytime in adulthood. This suggestion, however, is soundly contradicted by the patients' handedness because they were all RH persons, and this new hypothesis requires them to be NRH persons. How to reconcile this contradiction?

A single gene model with two alleles has been advanced for handedness and brain hemispheric laterality traits, and it neatly reconciles this contradiction. According to this random-recessive model, the *RGHT1* (for right-handedness) gene causes the dominant hemisphere to develop on the left side; consequently, a person exhibits RH preference since the left hemisphere controls right-hand actions [7]. And, in those individuals with both copies of the non-functional recessive *r* (for random hand preference and random brain laterality distribution) allele, brain laterality and handedness development are uncoupled, and both traits are distributed randomly and independently to the left or the right side of a person. Specifically, *r/r* individuals develop random hand preference; that is, 50% are RH and 50% are NRH [9] persons, and their brain laterality is independently and randomly distributed. Accordingly, this handedness genetic model postulates that breast cancer patients exhibiting random brain laterality, although selected by researchers to be RH, possess the *r/r* genetic constitution. Therefore, I suggest that brain laterality specification and breast disease traits likely share a common genetic etiology: specifically, the *r/r* genotype is proposed to be the primary predisposing factor for breast cancer disease in the white women subjects of the study.

5. How might the genetics of brain laterality development cause breast cancer disease in a minority of cases?

Only one specific hypothesis states that a single asymmetric cell division in the fetus dictates brain laterality specification. This "SSIS" hypothesis proposes somatic DNA strand-specific epigenetic imprinting to differentiate sister chromatids, followed by selective chromatid segregation in mitosis [10,11]. This hypothesis suggests that a left- versus a right-hemisphere-generating progenitor cell is produced at a specific asymmetric cell division in the embryo. We can speculate that the normally operating "developmental noise" resulting from stochastic errors in the SSIS processes might cause cancer in a minority of *r/r* individuals. In other words, predisposition to cancer likely originates as an anomaly of the mechanism of asymmetric cell division. For example, unwanted chromatid recombination in somatic tissues could interfere with the selective chromatid distribution postulated in the SSIS process. Indeed, loss of heterozygosity by mitotic recombination of imprinted (silenced)/expressed tumor suppressor genes is a well-known mechanism of cancer

causation. Alternatively, the *r/r* genotype may predispose carriers to develop disease-causing genomic rearrangements [12]. Regardless of how the genetic mechanism operates to specify these traits, their remarkable association raises the possibility that the same genetic cause might be responsible for brain laterality and breast cancer development. Likewise, profound cerebral asymmetry differences exist between homo- and heterosexual-human subjects [13], a result supporting the earlier suggestion that the *r/r* genotype comprises a predisposing factor for NRH, random brain hemispheric asymmetry, and for developing homosexual preference [14].

6. How to test the hypothesis?

The brain, skin, and skin-associated glands, including the mammary gland, derive from the ectoderm layer of the embryo. This is especially true for the breast epithelium, which is the component of the breast that contributes to breast cancer. It is easier to imagine that breast cancer develops not from embryonic events in utero, but rather from events in adult life. Although Sandson et al. [6] explained their results in favor of the hormone-exposure-in-utero hypothesis [8] for cancer causation, they also mentioned other possibilities: “Alternatively, an unidentified genetic, intrauterine, or early life factor could account for our findings.” Picking up where their report left off, it is suggested here that the same genetics predisposing individuals to develop NRH preference constitutes a primary predisposing factor, albeit with low penetrance, for a large proportion of sporadic cancer cases. It should be realized that the association between seemingly unrelated traits does not necessarily establish their common causality. However, this hypothesis is testable because it predicts that NRH women will have a higher incidence of breast cancer than RH women. Supporting this hypothesis, left-handed women are more than twice as likely than RH women to develop premenopausal breast cancer [15].

To emphasize the importance of the Sandson study [6] to the field of breast cancer research, a focus on the remarkable association between seemingly unrelated traits is critical because such associations will help define etiology of breast cancer. Clearly, the biological basis of the association between these traits has been previously unappreciated, but when identified, such associations should help direct future research efforts to diagnose and treat human disease.

At the very least, it is critical to independently replicate this sole study, as well as to conduct similar investigations with subjects of other ethnic groups. Also, the data cited [6] concern sporadic breast cancer cases only. If *r/r* genotype is also the basis of familial incidence in non-*BRCA1/2* families, determining brain laterality and handedness of families with increased risk represents another test of the model. Given that there may be unknown genetic risk factors in sporadic cases, it would be interesting to determine whether the correlation between brain laterality and breast cancer risk is the same or different in sporadic and familial cases. If the research is replicated and extended, the most significant genetically determined breast cancer risk factor would become apparent. Furthermore, such research might be extended to other kinds of sporadic cases of cancer.

Last, the 19-year-old study [6] has not been followed up perhaps because results are thought to be fully explained by the intra-utero hormone exposure hypothesis. I advance here an alternative genetic hypothesis. Clearly, further work is needed to define causality for each trait, to replicate the initial study, and to explore the reason for the remarkable association between these traits.

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Table 1

Brain laterality of subjects (Sandson, Wen and Lemay, 1992)

# subjects	Frontal width			Occipital width		
	L > R (reversed)	L = R	R > L	R > L (reversed)	R = L	L > R
97 controls	18%	18%	65%	18%	10%	72%
67 patients	49%	19%	31%	49%	21%	30%

L, Left-, R, right-hemisphere.