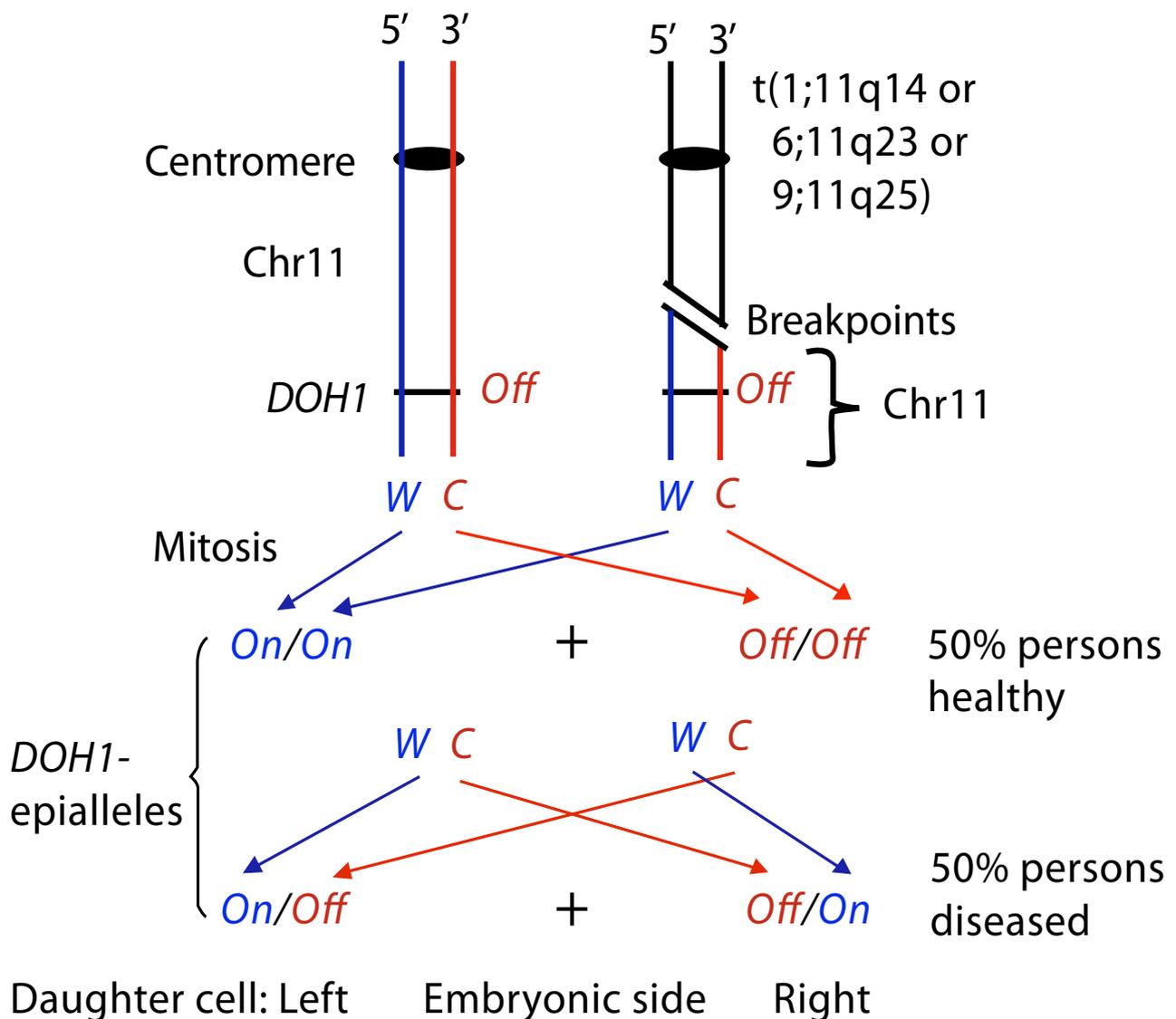


Selective chromatid segregation mechanism explains chr11 translocation causing psychoses with 50% penetrance

Brain hemispheres laterality-generating cell



Selective Chromatid Segregation Mechanism Explains the Etiology of Chromosome 11 Translocation-Associated Psychotic Disorders: A Review

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Abstract

The left and right hemispheres of the brain in most individuals are structurally and functionally specialized, but a significant minority displays an atypical variation in brain laterality specialization. Determining the biological basis of laterality specialization is essential for understanding the etiology of schizophrenia and bipolar disorder because they are often more prevalent in individuals with atypical brain laterality. These disorders are thought to be caused by contributions from hundreds of genes with small effects combined with environmental factors. However, lacking convincing evidence, the precise etiology of psychosis remains unknown. We have argued that chromosome 11 translocations associated with psychosis found in three families provide the only convincing evidence for the genetic etiology of psychosis. The paradoxes we try to resolve here concern the fact that the translocation breakpoints for chromosome 11 lie far apart, covering 40% length of the q arm, and the translocation associated psychoses is only 50% penetrant in each family. The selective chromatid segregation model has been proposed as a mechanism for the asymmetric cell division that initiates a cascade of gene regulation events in offspring cells to develop brain laterality in embryogenesis. The translocations we propose might cause random segregation of its sister chromatids to explain the result of 50% penetrance. We submit that errors in this system may explain the unique condition of these families. Here we review studies of model organisms that provide support to the model to explain brain laterality and psychosis development. We suggest that atypical brain laterality genetics predisposes carriers to develop general cases of psychoses due to developmental errors.

Keywords: Psychosis etiology; Selective chromatid segregation; Brain laterality development; Asymmetric cell division mechanism

Abbreviations:

SSIS: Somatic Strand-Specific Imprinting and Selective Sister Chromatid Segregation Mechanism; W: Watson DNA Strand; C: Crick Strand; DOH1: Dominant Hemisphere-Specifying Gene 1; RGHT1: Gene That Causes Right-Hand-Use Preference in Humans; r: Random Brain Hemispheric Laterality-Specifying Gene; LRD: Left-Right Dynein-Encoding Gene

Etiology of Psychosis Remains Unknown

The biological basis of human brain left-right hemispheric asymmetry development is an important and poorly understood aspect of human biology [1]. It is however clear that schizophrenia and bipolar disorders result from anomalies in brain laterality development. Schizophrenic patients experience imaginary voices and visions, and are unable to differentiate between what is real and what is imaginary, while bipolar subjects alternate between depressed and manic states. It is thought that these disorders are etiologically related brain development disorders, either disorder affecting approximately 1% of the population worldwide [1]. These are considered to be complex diseases caused by multiple genes with small effects in combination with environmental factors affecting an individual's upbringing. A most recent study by 300 authors received much popular media coverage [2]. This study employed genome-wide associations with approximately 37,000 psychoses subjects and 113,075

control subjects and suggested that at least 108 genes comprise the etiology of these disorders. In a recent review [3] interviews of prominent leaders of the genetic mapping field makes the same point that no major gene mutation has been implicated in the etiology of psychosis thus far. Despite this analysis, family and twin studies have been interpreted as favoring a large number of potential susceptibility-causing genes spread over many chromosomes.

Often these traits are suggested to have a genetic etiology because they run in certain families. Indeed, the "running in families" argument is usually advanced to lobby for further research proposing to recruit much larger numbers of selected families with higher disease incidence to determine genetic etiology with genome-wide association studies [2]. However, because all studies performed thus far on thus selected families have failed to discover a genetic mutation as the cause (though not for a lack of trying), we surmise that this argument is no longer valid to use in support of this type of research. And, because the etiology of psychiatric disorders remains unknown, little or no improvement in patient care has resulted from decades of research. Notably, none of the hundreds of studies claiming to find hundreds of single nucleotide polymorphisms associated with psychosis has been replicated. Considering this background, what is the convincing evidence, if any, supporting a genetic etiology for psychoses?

Chromosome 11 Translocations Reportedly Provide Convincing Evidence for Genetic Etiology

We have previously argued that no convincing evidence exists in support of a genetic etiology for psychosis, other than that of the three

families reported previously [1,4]. These families have very different balanced Chromosome 11 translocations, with unrelated breakpoints and with three other chromosomes involved (Figure 1). Notably, 18 of 36 t(11q14;1q42) [5], two of four t(11q25;6q14) [6], and six of 15 t(11q23;9p24) [7] heterozygous balanced translocation carriers developed psychotic disorders. Based on these findings, we made three conclusions/observations [1]. First, only Chromosome 11 is relevant as it is common to all families containing psychosis-associated translocations. Second, only one-half of translocation carriers are diseased. And third, the Chromosome 11 translocation breakpoints lie in regions located far from each other, covering approximately 40% of the long (q) arm of the chromosome (Figure 1). In light of the third point, it is unlikely that a single disease-causing gene has been mutated by three different translocations. Moreover, in all three translocation cases, follow-up studies failed to find genetic linkage between the translocation junction chromosome regions and inheritance of the disease in other families, those who do not have chromosomal rearrangements [8-10]. It was therefore proposed that psychosis might occur in translocation carriers without the presence of a mutated gene, although the translocations support the genetic etiology hypothesis because they involve chromosomes [1,4]. How is it possible to reconcile this internally inconsistent genetics-without-mutation etiology hypothesis? By far, t(11q14;1q42) is the most prominent translocation positing disrupted-in-schizophrenia-1 (DISC1) as the gene disrupted by the translocation breakpoint. By coining the term DISC1, one assumes that the mutation is truly disease causing; however, subsequent studies have not convincingly implicated this or any other gene in general cases of psychosis.

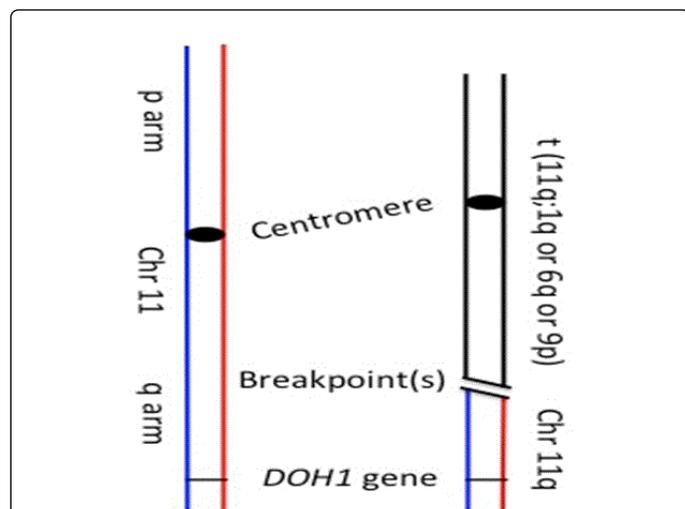


Figure 1: Chromosome 11 balanced translocations with Chromosome 1, Chromosome 6, or Chromosome 9 partners. Each of these translocations co-segregates with psychosis in approximately 50% of the heterozygous translocation carriers. The location of the translocation breakpoints and a description of the hypothetical dominant hemisphere-specifying (DOH1) gene are described in the text and the legend to Figure 2. The diagram is not drawn to scale.

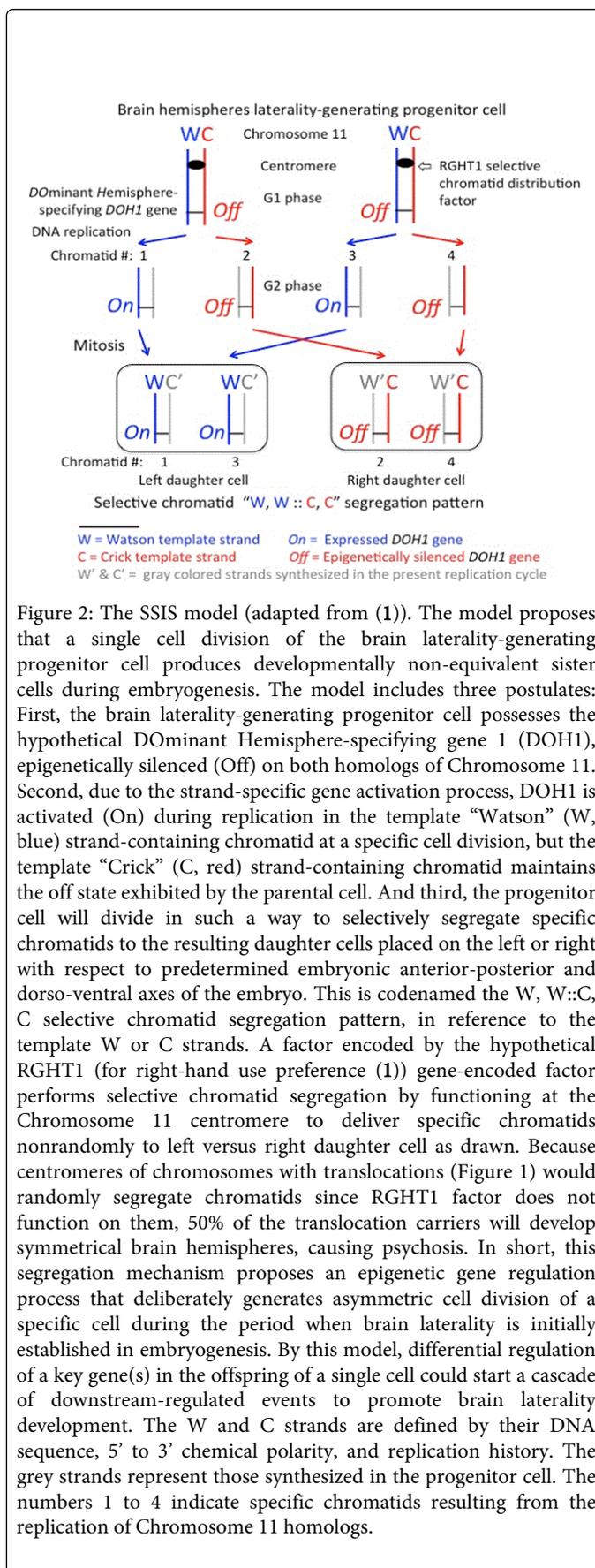


Figure 2: The SSIS model (adapted from (1)). The model proposes that a single cell division of the brain laterality-generating progenitor cell produces developmentally non-equivalent sister cells during embryogenesis. The model includes three postulates: First, the brain laterality-generating progenitor cell possesses the hypothetical DOminant Hemisphere-specifying gene 1 (DOH1), epigenetically silenced (Off) on both homologs of Chromosome 11. Second, due to the strand-specific gene activation process, DOH1 is activated (On) during replication in the template "Watson" (W, blue) strand-containing chromatid at a specific cell division, but the template "Crick" (C, red) strand-containing chromatid maintains the off state exhibited by the parental cell. And third, the progenitor cell will divide in such a way to selectively segregate specific chromatids to the resulting daughter cells placed on the left or right with respect to predetermined embryonic anterior-posterior and dorso-ventral axes of the embryo. This is codenamed the W, W::C, C selective chromatid segregation pattern, in reference to the template W or C strands. A factor encoded by the hypothetical RGHT1 (for right-hand use preference (1)) gene-encoded factor performs selective chromatid segregation by functioning at the Chromosome 11 centromere to deliver specific chromatids nonrandomly to left versus right daughter cell as drawn. Because centromeres of chromosomes with translocations (Figure 1) would randomly segregate chromatids since RGHT1 factor does not function on them, 50% of the translocation carriers will develop symmetrical brain hemispheres, causing psychosis. In short, this segregation mechanism proposes an epigenetic gene regulation process that deliberately generates asymmetric cell division of a specific cell during the period when brain laterality is initially established in embryogenesis. By this model, differential regulation of a key gene(s) in the offspring of a single cell could start a cascade of downstream-regulated events to promote brain laterality development. The W and C strands are defined by their DNA sequence, 5' to 3' chemical polarity, and replication history. The gray strands represent those synthesized in the progenitor cell. The numbers 1 to 4 indicate specific chromatids resulting from the replication of Chromosome 11 homologs.

SSIS Model Proposed for Generating Asymmetric Cell Division Required for Brain Laterality Development

One of the central questions of developmental biology addresses the mechanisms that produce asymmetric cell division at critical times during embryogenesis. Multiple mechanisms of asymmetric cell division are described from studies of model organisms, such as worms, flies, and yeasts [11,12]. Diverse mechanisms have been entertained, such as unequal distribution of cell fate factors (RNA or proteins, for example) to daughter cells by the parent cell and/or by uneven exposure of daughter cells to the microenvironment. Different mechanisms are likely to have evolved to accomplish cellular differentiation in diverse systems. The selective strand-specific imprinting and selective chromatid segregation (SSIS) model (Figure 2) was proposed as one of the mechanisms to deliberately produce asymmetric cell division, as well as to form the basis of human brain laterality development [1]. This model was proposed to coordinate the distribution of DOH1 “epialleles” in mitosis at a specific stage in development (Figure 2). Indeed, the SSIS model was first proposed [4] to explain the nearly 50% psychotic disorder incidence in the t(11q14;1q42) carriers (Figure 1) described above.

The same model was subsequently advanced to explain the approximately 50% incidence of disease occurrence in the t(11q25:6q14) and t(11q23:9p24) heterozygous balanced translocation carriers also described in figure 1 [1]. Specifically, to explain the 50% penetrance, it was proposed that, while Chromosome 11 chromatids undergo selective chromatid segregation, chromatids of the rearranged chromosomes follow random distribution because their centromeres only support random chromatid segregation (Figure 3). Because of random chromatid segregation, 50% of embryos will have asymmetric cell divisions during embryogenesis and will result in healthy subjects, while 50% will experience symmetric cell divisions and be diseased. Specifically, those embryos that undergo symmetrical cell division would produce symmetrical brain hemispheres, leading to the development of psychosis in the resulting adults. Thus, the 50% disease penetrance result of all three translocations strongly supports the SSIS model as a biological mechanism for brain laterality development in humans. The SSIS mechanism has been also invoked to explain the origin of congenital mirror hand movement disorder found to occur with 50% penetrance in human subjects with the rad51 heterozygous constitution [13].

Each Mouse Brain Hemisphere Likely Derives from the Offspring of a Single or Small Number of Related Cells

The brain hemispheric asymmetry in the frog is set as early as the 2-blastomere stage of the embryo, but it is unknown when visceral organ and brain hemispheric asymmetries are initially set during mammalian embryogenesis [reviewed in [14-16]. The SSIS model was specifically proposed to explain the biological basis of left-right laterality development, first for visceral organs and subsequently for brain hemispheres, by specifying asymmetric cell divisions at certain stages in mammalian embryogenesis. Accordingly, the model postulates that each brain hemisphere derives from the offspring of a single left- or right-side-specialized cell. Wu et al. [17] recently described a transgenic mouse line in which they inserted a red fluorescent protein-encoding reporter gene into one X chromosome and a green reporter gene into the other. Only one or the other fluorescent marker is expressed in individual mouse cells due to the inactivation of one of the two X chromosomes. As expected, random

chromosome activation occurs at each cell division in most of the mouse tissues and the paternal chromosome was activated in the extra-embryonic tissue.

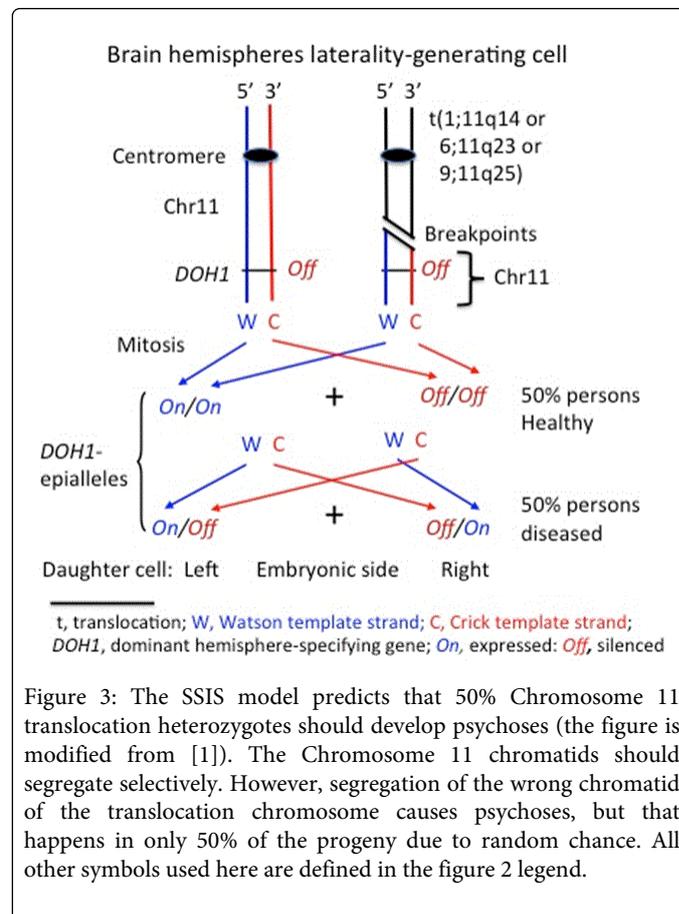


Figure 3: The SSIS model predicts that 50% Chromosome 11 translocation heterozygotes should develop psychoses (the figure is modified from [1]). The Chromosome 11 chromatids should segregate selectively. However, segregation of the wrong chromatid of the translocation chromosome causes psychoses, but that happens in only 50% of the progeny due to random chance. All other symbols used here are defined in the figure 2 legend.

Unexpectedly, however, ectoderm layer-derived tissues, such as excitatory neurons in the cortex and hippocampus, expressed only a single X chromosome in each organ of the animal. For example, the excitatory neurons of the entire brain hemisphere displayed primarily the red color while the other hemisphere developed primarily green-colored neurons in five of the 16 embryos examined. Not all embryos are alike is because a random activation of either X chromosome occurs in each brain hemisphere. Therefore some embryos probably express green colored while others probably express red colored neurons in both hemispheres. These results are consistent with the idea that the mouse brain hemisphere develops from the offspring of a single cell, as uniquely postulated in the SSIS model (Figure 2). By this hypothesis, an asymmetric cell division early in development might establish a transcriptional cascade by activating a specific gene in a cell and its offspring cells, resulting in brain laterality development by offspring during embryogenesis. For example, the left-sided MI motor neuron and the right-sided eD3 epithelial cell in the *Caenorhabditis elegans* pharynx result from the asymmetric division of a single blastomere cell, a cell that had divided several cell divisions earlier before these lateralized cells are born during embryogenesis [18].

Evidence for the Sister Chromatid Differentiation Postulate of the SSIS Model Discovered in Fission Yeast

The SSIS model (Figure 2) postulates that the epigenetically differentiated sister chromatids of a specific chromosome, or a set of specific chromosomes, are produced at specific mitosis in development. The specific chromatid differentiation is based on the asymmetry of their DNA strands and by their replication history. For technical reasons, it is nearly impossible to determine the existence of such a phenomenon in higher cells. Which chromosome to test, which cell type and division to examine, and how to differentiate sister chromatids are several of the unknowns that prohibit discovery of the SSIS model in higher organisms. The chromatid differentiation postulate of the model has been only tested and demonstrated in two evolutionarily unrelated fission yeast model haploid organisms: *Schizosaccharomyces pombe* [19,20] and *Schizosaccharomyces japonicas* [21]. Following mitosis, these yeasts produce one daughter cell that changes its cell type while the other maintains the parents' cell type. Remarkably, this asymmetry is based on inheriting epigenetically differentiated sister chromatids from the parental cell (reviewed in [12]). Indeed, thus far only studies on the cell/mating-type switching phenomenon have tested and established the chromatid-based epigenetic mechanism of cellular differentiation. To exploit such an epigenetic control for cellular differentiation by diploid organisms, however, selective segregation of differentiated sister chromatids from both chromosome homologs would be required (Figure 2). Exactly this rationale was advanced previously to explain laterality development in the brain and visceral organs, as well as for explaining psychotic disorders associated with the Chromosome 11 translocations reviewed here.

Evidence Supporting the Selective Chromatid Segregation Postulate of the SSIS Model

The second unique postulate of the SSIS model (Figure 2) is that the chromosome-specific selective chromatid segregation mechanism operates in diploid cells whenever an asymmetric cell division is evolutionarily required for tissue homeostasis and for embryogenesis. Does the selective chromatid segregation phenomenon exist anywhere in biology? Curiously, all 432/432 Chromosome 7 G2 mitotic recombination events resolve so that each daughter cell inherits one recombined chromatid from the parental cell [22]. Normally, 50% of mitotic events should be of this type because chromatids would be segregated to daughter cells in an unbiased manner. So, how could recombination events promote selective chromatid segregation in mitosis? We suggested that mouse embryonic stem cells employ Chromosome 7 specific machinery for selective strand/chromatid segregation that segregates both template "Watson" (W) strand-containing daughter chromosomes/chromatids to one daughter cell and both older "Crick" (C) strand-containing ones to the other daughter cell regardless of recombination (the designated W, W::C, C segregation pattern described in Figure 2). Using this mitotic recombination system, we observed that the segregation mode varies with the cell type. For example, neuroectodermal cells exhibit the selective W, C::W, C pattern, whereas pancreatic, mesodermal, as well as cardiomyocytes, displayed random chromatid segregation [23]. Moreover, we found that those cell types exhibiting the selective segregation mode expressed the LRD gene, which encodes left-right dynein, a motor protein implicated in embryonic left-right specification, while those undergoing random segregation did not. Furthermore, RNAi-mediated LRD-knockdown in cells of the type

undergoing selective segregation caused them to adopt the random mode [24]. Because the cell type and LRD knockdown alters the segregation pattern, the Chromosome 7 recombination results provide several lines of evidence supporting the selective chromatid segregation postulate of the SSIS model.

Using cytological methods, a recent study demonstrated biased (85:15) chromatid segregation of sex chromosomes in asymmetrically dividing male *Drosophila* germline stem cells [25]. Although an interesting finding, the significance of this biased segregation remains unknown. In addition, we noted that all three autosomes segregate with the W, W::C, C (Figure 2) pattern [26]. Together, these mouse and *Drosophila* studies demonstrate the existence of the selective segregation processes in cells of diverse organisms. Therefore, these developments justify relabeling the SSIS model as the SSIS mechanism.

Atypical Brain Laterality-Specifying Genetics may Constitute the Predisposing Genetic Factor in General Cases of Psychotic Disorders

The above discussion only concerns Chromosome 11 translocation-associated psychosis. However, general cases of psychosis are known to not involve chromosome translocations. So, what is their etiology? Interestingly, persons with psychosis are approximately twice as likely to be left-handed than the general population. We therefore hypothesized that atypical brain laterality-determining genetics is the predisposing factor for general cases of psychotic disorders [1]. According to our random-recessive model, the postulated RGHT1 (for right-handedness) gene is responsible for coupling the development of handedness to brain hemispheric structural and functional asymmetry, such that language processing occurs in the left hemisphere due to invariant asymmetric cell division through the SSIS mechanism (Figure 2). By this model, homozygous *r/r* (*r* for random brain laterality development) individuals carry the nonfunctional allele of the RGHT1 gene. The *r/r* embryos would also follow W,W::C,C distribution but the specific chromatids are segregated randomly to the left versus the right daughter cell in the embryo (Figure 2). And therefore, inverted hemispheric brain laterality develops in one-half of *r/r* individuals (reviewed in [27]). Additionally we hypothesize that this *r/r* atypical brain laterality-specifying genetics constitutes the predisposing genetic factor to cause sporadic cases of psychosis. For example, the disorder is postulated to develop due to mitotic recombination occurring in Chromosome 11 in a minority of *r/r* embryos, thus interfering with the selective distribution of the DOH1 epialleles essential for the standard lateralized brain development (Figure 2). Thus Chromosome 11 translocations (Figure 1 and 3) and predicted Chromosome 11 mitotic recombination events can cause disease by interfering with proper distribution of DOH1 gene epialleles via the SSIS model (Figure 2). A similar mitotic recombination model of genetic predisposition has been advanced to explain the increased incidence of sporadic cases of breast cancer in women (those presumed to carry the atypical brain laterality-specifying *r/r* genetic constitution) through the loss of heterozygosity of tumor suppressor genes [28].

Conclusions

Asymmetric positioning and morphology of organs in animals, such as brain hemispheres in humans, indicate left-right body asymmetry. The major model for body laterality development postulates the distribution of morphogen gradients across the embryo,

but it has remained a controversial model, despite decades of research, due to a lack of convincing evidence supporting it [16]. We have obtained cellular biology-based evidence supporting the SSIS mechanism for visceral organ laterality development in mice [14,15], and we have reviewed here the evidence supporting the SSIS mechanism for brain laterality development. Accordingly, we conclude that translocations cause psychosis by disrupting the distribution of DOH1 epialleles during mitosis, and, notably, not by creating disease-causing mutations at chromosomal breakpoints (Figures 1-3). In contrast, all other psychosis studies concerning translocations follow the paradigm that breakpoints must cause gene mutations and/or by position-effects on expression of nearby genes. Other models do not readily explain the 50% disease penetrance of all three translocations. Ours is a unique explanation invoking a chromosomally borne epigenetic mechanism that has evolved to produce differentiated sister chromatids to promote asymmetric development for development. Although SSIS is surely a genetics mechanism as it concerns chromosomes, neither a conventional gene mutation nor a conventional genetic cross is at play in it. Also it does not concern the parent-of-origin-specific chromosomal imprints, rather it concerns epigenetic processes functioning only in somatic cells to specify cell fate, such as those performed by MAR1 (SIR2, Sirtuin) factors first discovered in the *Saccharomyces cerevisiae* budding yeast [29]. Therefore, to help appreciate distinction of this new cell biological paradigm from the classical/Mendelian genetics paradigm, the SSIS process has been named as the mitotic genetics ("mitogenetic") process [28]. In sum, we have reviewed here relatively recent studies that support the SSIS mechanism as a way to explain how Chromosome 11 translocations may cause psychosis in 50% of heterozygous translocation-carrying subjects. This review is intended to shed light on the etiology of debilitating psychotic disorders in humans and to stimulate more widespread testing of the SSIS model proposed for eukaryotic development.

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