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A Genetic Mechanism Implicates Chromosome 11 in Schizophrenia and Bipolar Diseases

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ABSTRACT

The causes of schizophrenia and bipolar human psychiatric disorders are unknown. A novel somatic cell genetic model postulated nonrandom segregation of "Watson" *vs.* "Crick" DNA chains of both copies of a chromosome to specific daughter cells. Such an oriented asymmetric cell division causes development of healthy, functionally nonequivalent brain hemispheres. Genetic translocations of the chromosome may cause disease by disrupting the biased strand-segregation process. Only one-half of chromosome 1 and 11 translocation carriers developing disease were recently explained as a result consistent with the model (Klar 2002). Is chromosome 1 or 11 involved? Does the translocation breakpoint cause disease? Remarkably, two other unrelated chromosome 11 translocations discovered from the literature likewise caused disease in ~50% of carriers. Together, their breakpoints lie at three distinct regions spanning ~40% of chromosome 11. Thus, chromosome 11 is implicated but the breakpoints themselves are unlikely to cause the disease. The results suggest that the genetically caused disease develops without a Mendelian gene mutation.

SCHIZOPHRENIA and bipolar affective diseases are mysterious, debilitating psychiatric disorders, relatively common, each affecting ~1% of the population worldwide (for a recent review, see Kennedy *et al.* 2003). Persons with schizophrenia experience imaginary voices, visions, and disorganized thought, are unable to form social bonds, and are unable to tell what is real from what is imaginary. The causes of these mental diseases are not known. Numerous families, twins, and adoption studies suggest that genetic factors are of major etiological importance, but the mode of inheritance has remained unexplained by Mendelian genetic models. Despite the absence of positive identification of a gene(s) or chromosome region(s), the inheritance is thought to result from contribution of multiple genes, each contributing a modest increase in risk, along with contribution from environmental factors. Molecular linkage and association studies of family members have suggested numerous susceptibility loci covering many of the human chromosomes. Lacking replication, however, such findings have not been definitive. For example, when the data from large sets of studies covering different families were recently pooled, none of the regions produced consistent support for linkage in the majority of genome-screen projects for both schizophrenia (Lewis *et al.* 2003) and bipolar disorders (Segurado *et al.* 2003). Thus far, no disease-causing gene or consistent chromosome region has been identified. Certainly no disease gene variant has been identified (Kennedy *et al.* 2003). A search of the PubMed database with the query "schizophrenia genetics" produces >6400 hits. Despite the extensive literature, the cause remains elusive. Progress in mapping studies is lacking and infectious agents continue to be considered as possible causes of psychosis (Ledgerwood *et al.* 2003).

Although no confirmed locus or chromosomal region has been clearly identified, the consensus of the field is that it is primarily a genetic disorder (Kennedy *et al.* 2003). Is the consensus well founded? Given this prevailing view of the field, a fair question to ask is: What is the best evidence, if any, supporting a genetic etiology? It was recently pointed out (Klar 2002) that possibly the best evidence consists of chromosomes 1 and 11 balanced translocation, t(1q42;11q14), that partially cosegregates with disorders in a large Scottish pedigree (Evans *et al.* 2001). As no family member is diseased without the translocation, disease is clearly associated with the translocation. However, 18 (9 schizophrenic and 9 bipolar) among 36 translocation heterozygous individuals are affected (Figure 1). It remains a fascinating genetic puzzle to solve why the translocation-caused alteration is genetically dominant in some cases and recessive in the others, an observation equivalent to 50% penetrance. A conventional explanation of why some translocation carriers are diseased, while others are not, invokes the phenomenon of incomplete penetrance in which the translocation constitutes one of the predisposing factors and the occurrence of the disease is influenced by other environmental factors or dominant

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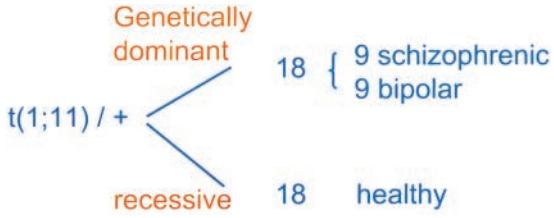

Figure 1.—Both dominant and recessive genetic aberrations caused by the same t(1q42;11q14) translocation (data from Evans *et al.* 2001). Curiously, among ill persons, one-half are schizophrenic and one-half are bipolar. The numbers indicate the number of persons in each category.

modifier(s) segregating in the family (Evans *et al.* 2001; Millar *et al.* 2003). According to this explanation, the translocation must have created a disease-predisposing mutation or misregulation of a nearby gene by epigenetic position effects. The junction region was molecularly characterized to test this hypothesis. Two divergently transcribed and overlapping transcripts were found to have a single base-pair mutation in chromosome 1 genes; hence, they were named *DISC1* (*di*srupted in *sc*hizophrenia) and *DISC2* (Evans *et al.* 2001). Studying the relevance of the breakpoint region for disease causation is well justified since cytogenetic abnormalities do cause dominant mutations resulting in other genetic diseases (Bassett 1992). However, experimentally testing the relevance of these mutations in t(1;11) as the cause of psychosis is rather difficult to achieve (Klar 2002). The *DISC1* and *DISC2* gene sequence and their mutations have not suggested their biological functions.

As another possibility explained in greater detail below, the observation of the 50% penetrance of the translocation in disease causation is consistent with a prediction of the newly advanced strand-segregation model (Klar 1999, 2002). Results of novel genetic tests of the model are presented here. Incidentally, it is often difficult to differentiate between these diseases owing to considerable overlap in their symptoms. Since one-half of the psychosis cases suffer from schizophrenia and the other half from bipolar disorder in the Scottish pedigree, both illnesses have been considered as manifestations of the same etiology (Crow 1990; DeLisi *et al.* 1997; Klar 2002). Accordingly, both disorders are considered here to result from the same cause.

RESULTS

The prevalence of psychosis in the Scottish pedigree is consistent with the somatic strand-specific imprinting and segregation model: The left and right human brain hemispheres are structurally and functionally different from each other in most individuals (Klar 1999). The mechanisms underlying the development of normal brain hemispheric asymmetry in healthy individuals and

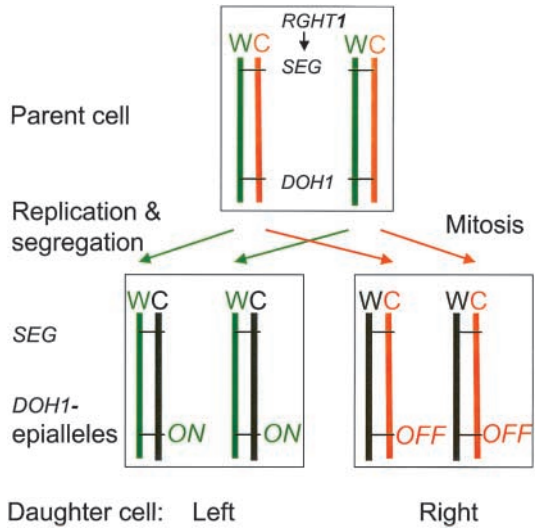

Figure 2.—The SSIS model to produce nonequivalent daughter cells by mitosis (expanded from Klar 1999). The model consists of three postulates: First, chromosome replication produces developmentally nonequivalent sister chromatids such that the hypothetical *DOH1* (*do*minant *h*emisphere specifying) gene is transcriptionally active (*ON*) in one specific, say parental chromosome-derived "Watson" (W)-strand-containing chromatid, and it remains inactive (*OFF*) by an epigenetic mechanism in the sister parental "Crick" (C)-strand-containing chromatid. For example, in a partially analogous situation, induction of the *HoxB* gene occurs in a DNA replication-dependent fashion and requires only one cell cycle for induction (Fisher and Mechali 2003). Second, a linked hypothetical *SEG* (*seg*regation) site exists elsewhere in the chromosome to effect patterned distribution of differentiated chromatids to specific ("leftward" *vs.* "rightward" placed with respect to dorsal/ventral axis of the embryo) daughter cells in the embryo at a specific cell division. Third, a *trans*-acting factor, encoded by hypothesized *RGHT1* (*right*-handedness) gene, acts on the *SEG* site directly, or indirectly, to nonrandomly distribute sister chromatids of both homologs to specific daughter cells. To better illustrate strand distribution, the parental chromosome W chains are green, C's are in red, and the newly synthesized chains are indicated in black. Colored arrows indicate the distribution of matching color-coded DNA chains and resulting chromatids to specific daughter cells. Note the asymmetric segregation of both parental W chains (green) to one daughter cell and both C's (red) to the other, while the newly synthesized complementary chains are indicated in black.

for the disturbance of cerebral asymmetry in psychotic patients remains unknown (DeLisi *et al.* 1997; Klar 1999). An unusual DNA strand-segregation model was proposed recently to explain development of lateralized, nonequivalent brain hemispheres in healthy individuals (Klar 1999; Figure 2). The model is based on the inherent nonequivalence of DNA chains, which are complementary in base sequence and possess the antiparallel chemical polarity according to the Watson and Crick double helix model (Watson and Crick 1953). As a consequence of a chromosome-based asymmetric cell division, one daughter cell inherits the *ON/ON* (transcriptionally active) *DOH1*, and the other inherits

the *OFF/OFF* (transcriptionally inactive) *DOH1* "epialleles" by inheriting thus "differentiated" chromatids. This occurs whenever the initial decision for producing asymmetric brain hemispheres is executed during embryogenesis. In short, the combinations of inherent sequence differences between DNA chains, postulated strand-specific somatic imprinting, and patterned segregation of differentiated chromatids of one or more chromosomes to specific daughter cells causes the development of nonequivalent brain hemispheres. Consequently, the left hemisphere develops as the so-called "dominant" language-processing hemisphere, while the right one develops as the "emotional" hemisphere in most individuals. Since diseased individuals show about threefold increased non-right-handedness (left- and ambidextrous-hand-use preference) *vs.* healthy controls (Boklage 1977), psychosis and non-right-handedness traits are significantly associated in an inexplicable way. Also, as there is reduction or reversal of normal anatomical and functional asymmetry in brain hemispheres in non-right-handers as well as in schizophrenia patients compared with right-hander controls (DeLisi *et al.* 1997), it has been suggested that psychosis might result from abnormalities of brain laterality development (Boklage 1977; Crow 1990; DeLisi *et al.* 1997; Klar 1999, 2002).

Genetic tests of the model: At first glance, it seems impossible to experimentally test the model, as it is not known which chromosome is involved, at what stage the postulated asymmetric cell division occurs during embryogenesis, and what the mechanism is for both strand-specific imprinting and patterned chromatid segregation. One novel test of the model concerns the study of genetic consequences of a chromosome translocation that unlinks the *SEG* site from the *DOH1* gene in one of the two homologs of the relevant chromosome (Figure 3). Thereby, random segregation of *DOH1* epialleles in the rearranged chromosome is expected, while the wild-type homolog undergoes patterned segregation. Consequently, one-half translocation heterozygote embryos should produce equivalent daughter cells, perhaps causing the development of symmetrical brain hemispheres, resulting in psychosis. This is a novel situation and it predicts that the translocation should be genetically dominant in one-half of the cases, resulting in diseased individuals, and recessive in the other half, resulting in healthy persons (Figure 3). Such an explanation, consistent with the model, was advanced in a recent study to explain the result of 18 diseased cases among 36 (*i.e.*, 50% penetrance) translocation heterozygotes (Klar 2002).

The unverified suggestion of the model is that disease stems not from mutation of any specific locus, but rather from altered segregation of *DOH1* epialleles. The model remains untested since from results with a single t(1;11)-containing pedigree it was not possible to determine whether or not chromosome 1 or 11 is involved. Nor was it possible to discount the conventional explanation

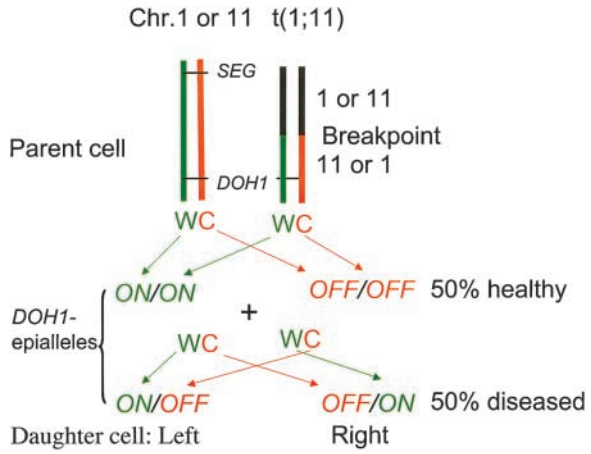

Figure 3.—A genetic prediction of the SSIS model (redrawn from Klar 2002). Genetic consequences of a translocation in the heterozygous constitution are diagrammed. The strands of the standard chromosome, be it chromosome 1 or 11, are segregated to daughter cells in a patterned fashion, as in Figure 2. However, because the rearranged chromosome lacks the *SEG* site, its strands should be randomly distributed to the daughter cells. Consequently, both daughters in one-half of the embryos will become equal, causing illness of only one-half of the translocation carriers. The symbols are the same as in Figure 2. Note the patterned chain distribution of the *SEG*-containing chromosome and a random distribution of the translocation chromosome.

that the breakpoint has caused a disease-causing mutation or an epigenetic modification altering the expression of a nearby gene (Klar 2002, 2003; Millar *et al.* 2003). Results verifying genetic predictions of the model are presented in Figure 3.

Tests of chromosome 1 *vs.* chromosome 11 and the translocation breakpoint for causing psychosis: This study was designed to determine whether missegregation of a portion of chromosome 1 or 11 in the translocation heterozygote is the culprit leading to psychosis. An equally important alternative addressed here is whether a genetic or epigenetic alteration at the breakpoint causes psychosis. The rationale pursued was that these questions would be answered by investigating the genetic consequences of other familial translocations, should they exist. Specifically, the model predicts that other translocations involving the relevant chromosome, be it 1 or 11, which unlink the *SEG* element from the *DOH1* locus, should also cause psychosis, but in only one-half of the translocation heterozygotes (Figure 3). However, translocations of the relevant chromosome with breakpoints lying outside the *SEG* and *DOH1* interval or those replacing *SEG* with an equivalent *SEG* site from the partner chromosome will not cause the disease and thus would not become a part of this database search study. Moreover, somatic rearrangements of the relevant chromosome are not transmitted to the progeny and they will also not become a part of this investigation.

TABLE 1

List of translocations causing psychosis

Translocation	No. diseased	No. healthy	*P*	References
1q42;11q14	18	18	>0.95	Evans *et al.* (2001)
17q21;11q23	1	0	—	Hoshi (1999)
6q14;11q25	2	2	>0.95	Holland and Gosden (1990)
9p24;11q23	6	5	>0.70	Baysal *et al.* (1998)

The number of diseased and healthy individuals for each translocation in a heterozygous constitution is tabulated. The *P* value noted for each pedigree was derived from the χ^2 test. These values suggest that the proportion of affected individuals is not significantly different from the 50% affected prediction of the model (Figure 3).

Many studies were found through a search of the PubMed database using the query "psychosis and translocation." As expected, dozens of research articles describing the aforementioned t(1;11) were found. Additionally, several articles describing other translocations were discovered (Table 1).

A t(17q21;11q23) translocation was reported in a case study of an acute leukemia patient who died during cancer treatment and who was also schizophrenic (Hoshi 1999). It is impossible to determine from that single case whether the translocation was indeed the cause of psychosis, as it may simply be a chance association between translocation and psychosis. Such a point was also made earlier to explain other single-case reports of psychosis described in the literature (Bassett 1992; Craddock and Owen 1994). However, while considering other pedigrees with multiple diseased members carrying other chromosome 11 translocations (Table 1), it seems worthwhile to consider the relevance of the t(17q21;11q23) translocation to the etiology of psychosis.

Although the number of individuals carrying other chromosome 11 translocations is small, as compared to the relatively large pedigree segregating t(1;11), these additional cases of translocations test and support the strand-segregation model in multiple ways and allow one to draw novel conclusions. First, as chromosome 11 is a common participant in these translocations, only chromosome 11 is considered relevant for psychosis and, by inference, for normal brain development when it is not rearranged. This search also discovered two other studies reporting examples of schizophrenia (Bassett 1992) and bipolar (Craddock and Owen 1994) disorders associated with cytogenetic abnormalities. Likewise, both of those studies highlighted the prominent involvement of chromosome 11 translocations in psychosis, but instead invoked the conventional explanation that the breakpoints must have created disease-causing mutations of different genes. Second, the observed 50% penetrance with three different chromosome translocations [t(1;11), t(6;11), and t(9;11)] satisfies a novel genetic prediction of the model (Figure 3) whereby translocations cause the disease in only one-half of heterozygous translocation carriers. This result strengthens the conclusion that psychosis in the translocation-containing families stems solely from a genetic etiology. Third, as the four sets of translocations involve three or four different chromosome 11 regions (q14, q23, and q25) located far apart from each other and covering ~40% of the linkage group, it is difficult to conclude that the breakpoints cause mutations or position-effect alterations of a single chromosome 11 locus. Fourth, the data suggest that the *SEG* and the *DOH1* genetic elements lie outside and flank the chromosome 11q14 to 11q25 interval. Fifth, the most novel aspect of this explanation is that the disorder in these families is due strictly to genetics, as it partially cosegregates with different translocations, but it is not due to a specific gene mutation. Additional independent results supporting the last conclusion are presented in the next section.

The translocation breakpoint regions are not linked to the disease in general cases of psychosis: The conventional explanation enthusiastically proposed by investigators working on each of these translocations was that the breakpoint creates a disease-causing mutation or position effect on a nearby gene (Holland and Gosden 1990; Bassett 1992; Craddock and Owen 1994; Baysal *et al.* 1998; Evans *et al.* 2001). But there is a major problem with this explanation. Namely, why is the translocation dominant in one-half of the individuals and recessive in the remainder (Figure 1)? Most relevant to this consideration, like the genetic behavior of the t(1;11) translocation, both t(9;11) (Holland and Gosden 1990) and t(6;11) (Baysal *et al.* 1998) also caused conventionally dominant as well as recessive genetic effects roughly equivalent to 50% penetrance (Table 1). To logically investigate the usual breakpoint-caused mutation hypothesis, all groups working on these translocations tested whether the molecular markers linked to the breakpoint in each set of participating chromosomes cosegregate with the disease in unrelated families with general cases of psychosis. The investigators of three such independent studies, concerning three different translocations, must have been puzzled when they obtained evidence against a nearby gene with a major

effect on random cases of psychosis (Devon *et al.* 2001; Baysal *et al.* 2002; Jeffries *et al.* 2003). Moreover, consistent with the somatic strand-specific imprinting and segregation (SSIS) model, no gene was interrupted by both junctions of the t(6;11) translocation. In contrast, the closest gene encoding β-1,3-glucuronyltransferase-1 situated 299 kb away is hypothesized to be a disease-predisposing candidate gene (Jeffries *et al.* 2003); once again, it is not clear how to test this gene's role in disease etiology. Also, a recent linkage study, initiated partly because of the presumed significance of chromosome 1 in the t(1;11) translocation in disease etiology, failed to implicate the chromosome 1q region in psychosis in a study of a very large multicenter sample of randomly chosen psychotic patients (Levinson *et al.* 2002). Collectively, these studies further support the conclusion of this study (see above) that the breakpoint regions of different translocations themselves do not cause the disease. In contrast, genetic heterogeneity, environmental reasons, and/or segregation of a genetic modifier have been proposed as conventional explanations for the reduced penetrance of the translocation rearrangement (Holland and Gosden 1990; Baysal *et al.* 1998; Evans *et al.* 2001). Moreover, further considering the modifier segregation hypothesis, it is unlikely that a single dominant modifier exists in heterozygous condition in all three families, which modifies the effect of mutations of three different genes, all in heterozygous condition, to result in ~50% penetrance (Table 1). Such explanations are commonly invoked in studies of complex traits but they are difficult, if not impossible, to verify experimentally as directed matings of humans are not an option.

Genetics of brain laterality development: One key aspect of the SSIS model derives from the earlier work with a simpler eukaryotic system of fission yeast. There a somatic genetic principle was established whereby mitotic chromosome replication produces sister chromatids that are different from one another (Klar 2001). Specifically, a DNA strand- and site-specific modification constitutes an epigenetic event that results in the production of nonequivalent sister chromatids. Their inheritance confers developmental asymmetry to daughter cells such that sister cells exhibit different sex/cell types. As yeast is a single-celled and haploid organism, no biological need can be perceived for a patterned DNA chain-segregation mechanism to evolve there. A similar model was advanced for producing asymmetric cell division to develop brain hemisphere laterality in humans by further postulating nonrandom segregation of chromatids of both homologs of a chromosome to daughter cells, now concluded here to be chromosome 11, in a certain cell division (Klar 1999). Consequently, an oriented asymmetric cell division results.

As stated above, two hemispheres of the human brain are nonequivalent in terms of morphology and function. The hemisphere that processes motor functions and often language is called the "dominant" hemisphere. Furthermore, 97% of right-handed individuals develop a dominant left hemisphere, whereas left- or ambidextrous-handed individuals develop a dominant left hemisphere in about one-half of the cases (Klar 1996). The model developed was that the *RGHT1* gene product functions, directly or indirectly, to cause patterned segregation of specific chains/chromatids to the left- *vs.* rightward placed daughter cells and also it couples the development of a dominant left hemisphere to right-hand-use preference (Figure 2). It was recently found that clockwise *vs.* counterclockwise orientation of scalp hair-whorl rotation and hand preferences develop from a common genetic mechanism (Klar 2003). Individuals homozygous for the nonfunctional recessive *r* (*r* for random, an allele of the *RGHT1* gene) allele might frequently cosegregate parental chromosomal Watson-with-Watson and Crick-with-Crick chains, but their distribution to the left *vs.* right hemisphere of the brain might be random. Also, a random distribution of hand preference, brain laterality, and scalp hair-whorl rotation traits is suggested to occur with respect to each other and to the left *vs.* right side of the body in *r/r* individuals. It therefore seems that the *RGHT1* gene controls the distribution of brain laterality, hand-use preference, and the orientation of hair-whorl rotation with respect to the left/right body axis (Klar 2003). One of the ways the *RGHT1*-gene product may function is by mediating patterned chain segregation during embryogenesis.

Does the patterned DNA strand-segregation phenomenon occur in biology? It is generally assumed that DNA chains are randomly segregated to daughter cells during mitosis. The SSIS model instead postulates the existence of a patterned segregation phenomenon. The question therefore arises: Does the phenomenon of patterned parental Watson *vs.* Crick chain segregation occur in biology? Two kinds of biased segregation mechanisms can be envisioned. First, an ingenious model (Cairns 1975) has been advanced as a mechanism for a cell to avoid DNA replication errors in rapidly regenerating tissues, such as skin, by segregating the "older" strands used as template for replication from each chromosome to a special "stem" cell that keeps generating new cells (Merok *et al.* 2002). Second, the SSIS model suggests that the parental Watson strands from both homologs cosegregate to a specific daughter cell; consequently, both Crick chains will be delivered to the other daughter cell (Figure 2). Furthermore, this process can be developmentally controlled to function at a specific cell division during embryogenesis and may involve one or a set of specific chromosomes (Klar 2001). Different sets of chromosomes may be similarly treated in cells of other cell types.

A possible case of biased segregation of chromatids, hence parental chromosome chains, was reported recently in a study of *Cre-loxP*-induced mitotic recombi-

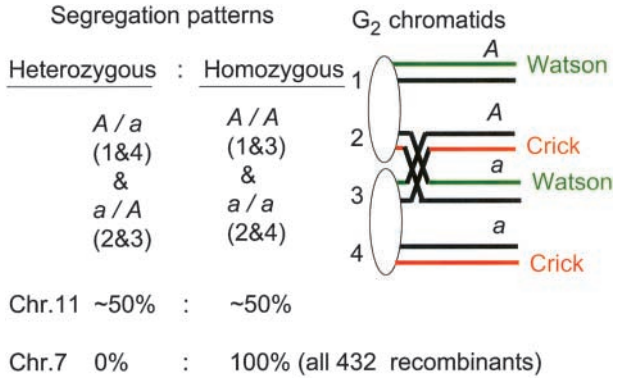

Figure 4.—A genetic test of the Watson-with-Watson and Crick-with-Crick cosegregation phenomenon in mouse embryonic stem cells (data from Liu *et al.* 2002). Mitotic site-specific recombination was induced with the *Cre-loxP* system by placing recombination cassettes at allelic sites near the centromeres of indicated chromosomes. Crossing over was induced by transiently expressing Cre-recombinase in mitotic dividing cells. Numbers 1–4 indicate specific parental chromosomal strands and the resulting chromatids of a G_2 cell. The oval figures reflect centromeres. The genetic constitution of distal markers (*A* and *a*) indicates the segregation pattern of a recombinant. To highlight chain distribution, only the parental chromosome strands are indicated in green and red, while black lines represent the newly synthesized strands in the resulting chromatids.

nants in mouse embryonic stem cells (Figure 4). The usual expected random chromatid distribution of one of the chromosomes was observed as nearly one-half G_2 recombinants maintained heterozygosity of the marker distal to the crossover point, and the other half acquired the homozygous constitution. Remarkably, however, all 432 G_2 recombinants of another chromosome resulted in homozygosis of the distal marker (Figure 4). The unusual mouse chromosome 7 result was explained by postulating that the exchange event itself affects subsequent orientation of homologous chromosomes at the metaphase plate, thus ensuring recombinant chromatids (2 and 3 in Figure 4) to segregate away from each other during mitosis (Liu *et al.* 2002). An alternative interpretation of the homozygosis result is advanced here; it may be that Watson-with-Watson and Crick-with-Crick parental chromosome chain cosegregation normally occurs for this chromosome, resulting in homozygosis of all recombinants. Thus, chromatids 1 and 3 normally segregate to one pole of the spindle, while 2 and 4 go to the other (Figure 4). Interestingly, the biased segregation result requires that only two specific chromatids can participate in recombination, one containing the parental Watson chain and the other containing the parental Crick chain (Figure 4). This consideration also implies that sister chromatids of both homologs are preoriented at the metaphase plate in a specific way constraining their participation in recombination. These results with mouse cells suggest that biased segregation mechanism is chromosome specific as only one of the two chromosomes tested undergoes patterned segregation.

To further explore the relevance of patterned chain segregation explanation for mouse chromosome 7 with the biased human chromosome 11 segregation proposal of the SSIS model, synteny between the mouse and human chromosomes was searched within the GenBank database. Intriguingly, two large and two small blocks, together covering ~36% of mouse chromosome 7, exhibit synteny with human chromosome 11 (http://www.ensembl.org/Homo_sapiens/syntenyview ? species=Mus_musculus&chr=11&x=27&y=7). Additionally, classical imprinted regions (*i.e.*, those showing the parent-of-origin effect) in the syntenic domains were searched. Curiously, both mouse chromosome 7 and human chromosome 11 contain the well-known *H19/IGF2* imprinted region located at the chromosome tip (Kitsberg *et al.* 1993). The synteny may be relevant to the validity of the SSIS model. By inference from the patterned segregation interpretation of the mouse chromosome 7 result, the human chromosome 11 chains might likewise be subject to the patterned segregation process at a crucial cell division for developing brain hemispheric laterality. The result of biased chromosome 7 chromatid/strand segregation in mouse cells provides additional support to the model. It is often found that imprinted genes are located in clusters in the genome perhaps to facilitate region-specific imprinting mechanisms (Kitsberg *et al.* 1993). It is possible that this conventionally imprinted region showing the parent-of-origin effect on gene expression may also harbor the *DOH1* gene that is somatically imprinted in a strand/chromatid-specific fashion during development. Alternatively, homologous chromosomes may be somatically attached to each other at the imprinted region or at the *SEG* region to promote patterned segregation of their chains. For example, the homologs show preferentially S-phase pairing in the chromosome 15q11–q13 imprinted domains in human T lymphocytes (LaSalle and Lalande 1996) and in the imprinted region at the tip of mouse chromosome 7 (Riesselmann and Haaf 1999).

DISCUSSION

The suggestion of the model and its supporting evidence is that psychosis results from a genetic mechanism in translocation-containing families, but without invoking a conventional Mendelian gene mutation. It should be noted that this conclusion should not be considered as a violation of Mendelian genetics rules. Mendelian genetics predominantly concerns studies of allele frequencies of gametes produced by meiosis. In contrast, the SSIS model concerns both the generation of chromosomally borne epialleles and their nonrandom distribution to daughter cells only in mitosis. Such a mechanism must have evolved for controlling gene regulation that is essential for cellular differentiation, which in

turn is required for eukaryotic development. For example, such a mechanism may be essential for developing the anterior-posterior, dorso-ventral, and left-right axes in multicellular eukaryotes. To highlight this concept and to distinguish it from the Mendelian genetics discipline, the term mitogenetics is advanced here for describing chromosomal/genetic principles concerning mitotic cells. Therefore, the SSIS model describes a principle of the mitogenetics discipline.

This analysis should not be interpreted to mean that all psychosis cases must result from cytogenetic anomalies. Considering the large number of psychosis cases reported worldwide, the paucity of genetic rearrangements associated with psychosis is noteworthy. In fact, it was found that none of 46 random schizophrenic cases checked by chromosome cytology had noticeable chromosomal abnormalities (DeLisi and Lovett 1990). Clearly, most cases of psychosis are not caused by translocations. Then, what causes general cases of psychoses? Curiously, psychotic patients are three times more likely to be non-right-handers as compared with the public at large, causing many investigators to suggest a non-right-handedness etiology as the predisposing factor (Boklage 1977; Crow 1990; DeLisi *et al.* 1997; Klar 1999, 2002). Therefore, it has been speculated that general cases of psychosis may be correlated with the genetics controlling the development of left- *vs.* right-hand-use preference (Boklage 1977; Crow 1990; DeLisi *et al.* 1997; Klar 1999, 2002). Individuals lacking the presumed gene for specifying right-hand preference frequently develop less asymmetric brain hemispheres, possibly predisposing them to developmental anomalies resulting in psychosis. More specifically, the random-recessive model (Klar 1996) proposed that the brain laterality results from the patterned segregation of chromosome 11 DNA chains (this study) by the *RGHT1* gene-encoded factor. Thus, according to the random-recessive model, nearly all psychosis cases in the general public might result from the *r/r* genotype predisposing a small percentage of individuals to develop the disease possibly due to anomalies in the development of brain hemispheric asymmetry. By this scenario, there is no mutation assuring disease development; the *r/r* constitution acts only as a predisposing genotype such that the disease occurs owing to "developmental noise" of the genotype (Klar 1999). Accordingly, the *r* locus would not have been mapped or cloned already as part of the standard genome scan mapping studies as only a fraction of *r/r* individuals are predicted to be diseased. The *DOH1* gene may be essential for viability and its mutation would therefore not perpetuate, thus escaping identification in prior studies.

An alternate possibility is that other mutation(s) in conjunction with the *r/r* genotype may cause psychosis. For example, a recent report summarized three studies providing supporting evidence of variable strength between several single nucleotide polymorphisms (SNPs) in the Dystrobrevin-binding-protein 1 gene with schizophrenia in Irish families. However, this association is significant in some studies, in one of them in only a single branch of the pedigree, while in several other studies replication failed altogether (van den Oord *et al.* 2003). Furthermore, some SNPs are associated with schizophrenia whereas others located in the interval are not, and a specific SNP significant in one study was not significant anymore in a follow-up study. With such serious problems with strongest association reported for any gene thus far, this locus is unlikely to remain significant in future replication studies.

It remains to be determined whether the *RGHT1*-encoded factor acts directly on the *SEG* site, as originally proposed in the model (Figure 2). Alternately, it might function to cause cellular asymmetry or global cerebral laterality by some other mechanism that sets the stage for the biased chain-segregation mechanism to operate by some other factor interacting with the *SEG* site. By this hypothesis, there may be less asymmetry developed in the *r/r* genetic constitution. Consequently, increased chances for random chain segregation ensue, resulting in psychosis. Accordingly, the relationship between psychosis and handedness is indirect and only a small proportion of *r/r* individuals will develop disease. As most *r/r* individuals are healthy, whole-genome association studies to map the disease-predisposing *r* allele are not expected to be fruitful. By this scenario, chromosomal regions implicated for psychosis in many studies (Kennedy *et al.* 2003) are likely to be false positive, statistical coincidences. Such an explanation is in accord with the lack of replication of linkage studies. In contrast to general cases, however, there is a direct relationship between psychosis and the *DOH1* and *SEG* elements in translocation-containing families. Thus, presently a convincing case for the genetic etiology of psychosis can be made only for chromosome 11 translocations that partially cosegregate with the disease in a very small number of pedigrees (this study), and the causes of general cases of psychosis remain unknown. Whether the *r/r* genotype alone, or only in combination with other mutation(s), causes psychosis needs to be experimentally tested.

It is not known how the two brain hemispheres are made biologically different from each other in healthy individuals. The strand-specific model advances the mechanism to effect differential hemisphere-specific gene regulation. The SSIS model predicts production of nonequivalent daughter chromatids causing the resulting daughter cells to become developmentally different from each other. In addition to the primary results of chromosome 11 translocations, the results of biased segregation of mouse chromosome 7 and its synteny to the human chromosome 11 provide unusual support to features of the model. Another concept advanced is that in addition to carrying genetic codons as the genetic material according to the double helix model (Watson

and Crick 1953), the Watson and Crick chains can carry additional heritable (epi)genetic information to be used for somatic cellular differentiation. It will be highly rewarding scientifically to investigate new cases of translocation carriers in these and other families. Considering such a novel mechanism for disease causation, more cytological studies should be advanced to larger pedigrees with multiple affected members. This study provides a new paradigm to understand the cause of these highly debilitating diseases. Clearly, much remains to be done to test molecular details of this mechanism. Unlike other explanations advanced thus far, the mitogenetic model attempts to explain the puzzle as to why each of the three translocations causes genetically dominant aberrations only in one-half of carriers.

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