Note

The Chromosome 1;11 Translocation Provides the Best Evidence Supporting Genetic Etiology for Schizophrenia and Bipolar Affective Disorders

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ABSTRACT

Genetics is assumed to cause susceptibility to psychosis, but no major locus has been identified. These disorders cosegregate with a chromosome 1;11 translocation in a Scottish pedigree where 50% of the carriers are diseased. A genetic model originally proposed to explain the basis of these illnesses predicts such an outcome.

THE article in the January issue of Trends in Genetics by Evans *et al.* (2001) is a timely review of the field of psychiatric genetics. It emphasizes the consensus emerging from decades of work in the field, namely that psychiatric illness results from the complex interaction of many genes conferring susceptibility, combined with the effects of environment influences. The evidence is based on family, twin, and adoption studies. Unfortunately, many exciting discoveries originally reporting identification of several loci whose mutations were thought to cause schizophrenia or bipolar affective disorder have not been confirmed by any subsequent study. Consequently, despite a large amount of work no genes involved in the etiology of these illnesses have been identified to date. To others not trained in the field, the consensus seems to have been arrived at mainly from negative results or from circumstantial evidence. For example, as no major locus has been implicated, it is concluded that the disease must result from mutations in any one of several loci. Second, most cases of these disorders are sporadic, that is, only a single member of the family is diseased (Klar 1999), a finding arguing against the genetic mode of inheritance. Third, since monozygotic twins in the general population are often discordant, in that only one member of the pair is affected (Boklage 1977; Petronis 2001), environment is thought to play a role, too. So, what is the best evidence, if any, favoring genetics as the cause of major psychosis? Thus far, the mode of inheritance of major psychiatric diseases has remained unexplained by the simple genetic models. This remains a key unanswered question in the field.

The strongest evidence for a genetic basis consists of a balanced chromosome 1 and 11 translocation, t(1;11), that segregates with the disorders through multiple generations in a large Scottish pedigree (St. Clair *et al.* 1990; Blackwood *et al.* 2001) with a LOD of 6.0 (Millar *et al.* 2000). The data were collected by sampling the pedigree at different times spanning a period of over 30 years, and interestingly, only about one-half (a total of 18 among 36) of the translocation carriers were found to be diseased. Clearly, the disease must be caused by the translocation as none of the noncarriers are afflicted. However, there is a major difficulty with the conventional genetic explanation in which the translocation creates at the junction a disease-causing mutation(s) that directly affects or influences a nearby gene by position effect (Millar *et al.* 2000, 2001; Blackwood *et al.* 2001). Such an explanation requires the rearrangement to create a mutation that is dominant to the wild-type allele in one-half of the cases and recessive in the remainder, the basis for which has no obvious explanation. The observation that one-half of the individuals develop the disorder is usually explained by the ill-defined, often-invoked phenomenon of incomplete penetrance. This term is used when the disease does not develop in individuals carrying the disease genotype. Without any mechanistic support, incomplete penetrance seems an unlikely explanation given the observation of a 1:1 ratio of affected to unaffected individuals. In principle, another explanation may be that a dominant modifier whose inheritance represses the development of the disease in translocation heterozygotes is present in the general population at ~0.3 gene frequency. Here, I propose an alternate explanation in

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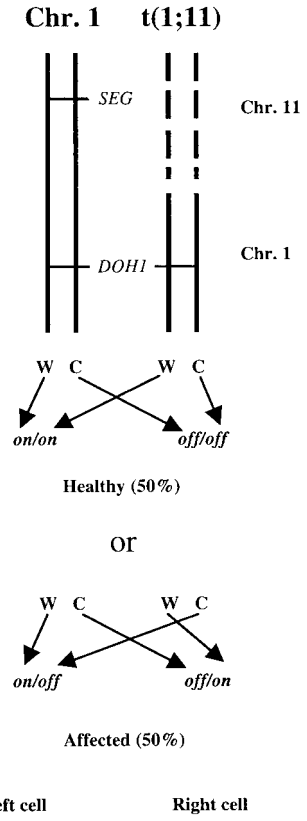

Figure 1.—A genetic prediction of the strand-segregation model involving the t(1;11) translocation. The strand-segregation model (figure modified from Klar 1999) predicts that only one-half of the translocation heterozygotes will develop the disease as t(1;11) parental strands will be randomly distributed (indicated by arrows) to the left- and right-ward placed daughter cells with respect to dorso-ventral body axis. *DOH1* is a hypothetical dominant hemisphere-specifying gene. *DOH1* and the *SEG* elements are arbitrarily placed on chromosome 1 (solid lines), but they could be located instead on chromosome 11 (broken lines). W, arbitrarily designated "Watson" chain; C, the "Crick" strand. *on* and *off* epialleles of the *DOH1* gene result from a differential chromatid-specific, somatic cell-imprinting event at a specific cell division during embryogenesis.

support of a genetic model explaining 50% inheritance of the trait.

An unconventional DNA strand-segregation model was proposed earlier to explain the cause of these disorders (Klar 1999). First, in this model (see Figure 1), two sister chromatids of chromosome 1 or 11 are "differentiated" by epigenetic means such that the hypothetical *DOH1* (for *do*minant *h*emisphere) gene required for body laterality, such as for specifying a dominant (language-processing) brain hemisphere, is expressed (*on*) in a DNA strand-specific fashion in one chromatid, but turned *off* by imprinting in the sister chromatid. Second, the model proposes that an unlinked segregation (*SEG*) site exists elsewhere in that chromosome, not necessarily at the centromere, to facilitate nonrandom distribution of "differentiated" chromatids in mitosis to daughter cells at the time in development whenever the brain laterality is originally set. Third, a *trans*-acting function encoded by another hypothesized *RGHT* (for *r*ight hander) gene acts on the *SEG* site to nonrandomly distribute sister chromatids of chromosome 1 during cell division. Thus, both *on*-containing chromatids are segregated to the same daughter cell, while both *off* "epialleles" are delivered to the other daughter cell. The *on/on* cell will specify the brain hemisphere that develops language cognition, while the *off/off* configuration will specify the hemisphere where language is not processed. Briefly, the model proposes asymmetric mitotic DNA strand segregation at a specific cell division during embryogenesis of humans.

A genetic test of the model is provided by the chromosome 1;11 translocation by postulating that the rearrangement separates the *DOH1* gene from the *SEG* site. Consequently, in translocation heterozygotes the translocation-containing chromatids that carry the *DOH1* gene but not *SEG* will be distributed randomly to daughter cells, while chromatids of the standard chromosome will be segregated normally (Figure 1). Thus, in one-half of the cases both daughter cells are predicted to inherit *on/off* epialleles and the individuals should develop psychosis. In short, the disease state is caused by the separation of *DOH1* from *SEG*, thus randomizing the distribution of the epialleles of *DOH1*.

This model makes other predictions. First, any heterozygous translocation involving the relevant chromosome, be it 1 or 11, should cause the disease in 50% of carriers, as long as it separates the two loci. Second, an inversion of *DOH1* or the *SEG* site individually in one chromosome should cause illness of *all* heterozygote individuals, but inversion-containing homozygotes should be healthy. Third, translocation heterozygote monozygotic twins should be discordant for the disease in one-half of the cases, provided that the critical cell division for brain hemisphere development occurs after twin formation. In contrast, according to the dominant-modifier model considered above, concordance should result; both members would be healthy if they inherit the modifier, and both would be diseased if they lack it.

Interestingly, one-half of the psychosis cases with the translocation suffer from schizophrenia and the other half from the bipolar affective disorder (Evans *et al.* 2001). Thus, there is a lack of disease-specific inheritance, as the propensity for either schizophrenia or bipolar disorder is inherited in the Scottish pedigree. Therefore, both disorders should be considered as manifestations of the same disease.

Conceptually, the model is an extension of the model established for mating-type switching in fission yeast. Inheritance of specific chains of the parental chromosome confer developmental asymmetry to daughter cells, resulting in mating-type switching of only one of the daughter cells (Klar 1987, 2001). This model has been extended to explain handedness by postulating a *RGHT* gene for nonrandom distribution of specific chromatids to daughter cells at a specific cell division

(Klar 1999). Such a model was first proposed for the left/right-visceral specification of mice (Klar 1994). By this explanation, the t(1;11) translocation causes psychotic disease simply due to random distribution of sister chromatids; no essential gene required for brain development is mutated. In contrast, Millar *et al.* (2000, 2001) and Blackwood *et al.* (2001) pursue a conventional explanation whereby the breakpoint causes mutations of two genes on chromosome 1, resulting in illness. Other families with psychosis could be examined for the presence of different translocations. Translocations with different breakpoints will falsify the current alternative that gene lesions at the t(1;11) translocation breakpoint are responsible.

It needs to be highlighted that this translocation is the best evidence supporting a genetic etiology for schizophrenia and bipolar affective disorders in the Scottish pedigree. This is not to say that other cases of psychosis in the general population must also result from such translocations. Instead, the strand-segregation model proposes that psychosis in individuals not carrying the translocation results from lack of the *RGHT* gene, predisposing some of those individuals to develop bilaterally symmetrical brains (Klar 1999). That the translocation causes illness in one-half of the translocation carriers should be considered as suggestive evidence favoring the strand-segregation model. Clearly, more work is needed to find the cause of these debilitating diseases, but the explanation proposed here should be helpful in designing more focused studies based strictly on a genetic etiology.

Note added in proof: A recent article eliminated the possibility of the translocation creating a disease-causing mutation, as the translocation junction region shows no association with the disorder in many other affected families without the translocation (R. S. Devon, S. Anderson, P. W. Teague, P. Burgess, T. M. J. Kipari *et al.*, 2001, Identification of polymorphisms within Disrupted in Schizophrenia 1 and Disrupted in Schizophrenia 2, and an investigation of their association with schizophrenia and bipolar affective disorder. Psychiatr. Genet. **11:** 71–78).

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