

PERSPECTIVES

Chance in our strands?

QUASAR SALEEM PADIATH^{1*} and B. JAGADEESHWARA RAO^{2*}

¹Dept. of Neurology, University of California, 505 Parnassus Ave., Box 0114, San Francisco, Ca., 94143-0114, USA

²Department of Biological Sciences, Tata Institute of Fundamental Research, Homi Bhabha Road, Mumbai 400 005, India

Bipolar disorder and schizophrenia are severe forms of mental illness that affect nearly 2% of the population world-wide. Although these psychiatric disorders represent distinct entities, considerable overlap in their clinical presentation may suggest a common causative mechanism. Decades of research have proved conclusively that both diseases have a strong genetic component. The diseases tend to run in families and first-degree relatives have a significantly higher risk of developing the illness compared to the general population. Identical (monozygotic) twins also have a much higher chance of both having the disease when compared to non-identical siblings. While the genetic component is in little doubt, elucidating the genetics of these diseases has proved to be much more complex and difficult to understand. This is because both bipolar disorder and schizophrenia are believed to be caused by the action of many genes with variable effects rather than a single gene. This is further complicated by interactions of these genes with the environment. Thus, individuals may inherit only the susceptibility to develop the disease rather than the disease itself.

What then are the genes that confer susceptibility to bipolar disorder and schizophrenia? Researchers have applied gene-hunting techniques that have been successful in discovering the genes for relatively rare single gene disorders like Huntington's disease and cystic fibrosis. They used large families with multiple affected individuals and identified specific chromosomal regions that were inherited along with the disease phenotype. The next step of identifying the specific disease causing mutations in these chromosomal regions, however, did not turn out to be entirely successful. Mutations found only in individuals carrying the disease were never identified.

Mutations or polymorphisms in genes that were thought to confer risk for the diseases in one population did not turn out to have any association with the disease in other populations (Evans *et al.* 2001). While there are many interesting candidate genes, we are yet to identify any genetic

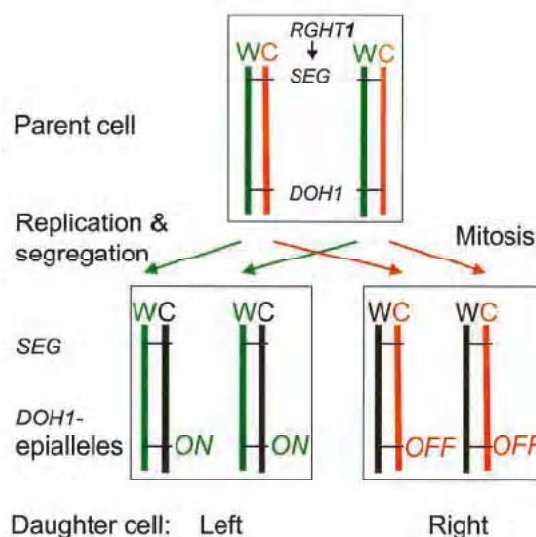


Figure 1. The SSIS model to produce nonequivalent daughter cells by mitosis. (Reproduced from: A genetic mechanism implicates chromosome 11 in schizophrenia and bipolar diseases. Klar A. J. 2004 *Genetics*. **167**, 1833–1840.)

mutation or variation that is unequivocally associated with either schizophrenia or bipolar disorder. How, then, does one explain the fact that no causative genes have been found for these genetic disorders?

As mentioned earlier, the widely held explanation is that these diseases are not caused by variations in a single gene, but rather by alterations in multiple genes with variable effects. Variations in these genes may interact among themselves and with the environment to produce a disease phenotype. Thus, one would have to study the effect of variations in multiple susceptibility genes simultaneously to understand the disease mechanism.

But could this be the only explanation? In a recent review, 'A genetic mechanism implicates chromosome 11 in schizophrenia and bipolar diseases' *Genetics* 2004 **167**, 1833–1840, Amar J. Klar has suggested a novel and unorthodox mechanism to try and explain the vagaries of psychiatric genetics. The hypothesis arises from his earlier work with the fission yeast, *Schizosaccharomyces pombe*. He suggests that these diseases may arise not from variations

*In keeping with the spirit of the article on which this perspective is based, a coin was tossed to decide the order of authors. They may be contacted at: qpadiath@itsa.ucsf.edu and bjrao@tifr.res.in.

or mutations in genes but rather from heritable changes that affect gene expression and function without changing their DNA code. Such epigenetic mechanisms are well known in cases of genomic imprinting, where genes behave differently depending on their parent of origin. Klar has also shown earlier that epigenetic mechanisms play a role in determining mating type switching in *S. pombe* (Dalgaard and Klar 2001).

How does mating-type switching in *Schizosaccharomyces* provide clues about schizophrenia? Klar uses the following observations to link the two. Some studies have suggested that there is an increased incidence of disease in individuals that are not right handed (i.e. left handed and ambidextrous). These nonright-handed individuals are thought to have a reduction or reversal of normal anatomical and functional asymmetry in brain hemispheres, a feature also seen in schizophrenia and bipolar disorder. Therefore a mechanism that leads to a loss of asymmetry in brain hemispheres may also play a role in the development of schizophrenia and bipolar disorder. It is this mechanism that Klar suggests may be under epigenetic control. The basic premise of Klar's hypothesis stems from his contention that the two complementary (Watson and Crick) strands of DNA are not equivalent if during mitosis a pair of disease relevant homologous chromosomes (WC & W'C') exhibit an intrinsic propensity to cosegregate parental Watsons (W, W') into one daughter cell and parental Cricks (C, C') into another (following replication, along with their newly made complementary strands). If a hypothetical gene, *DOH1* (the Dominant Hemisphere-specifying), was active only when both the Watson (or Crick) strands paired together, such mitosis would generate daughter cells that are genetically non-equivalent. Klar suggests that it is such an asymmetric cell division that occurs during embryogenesis to produce functionally and structurally unequal brain hemispheres. When this somatic strand-specific imprinting/segregation (SSIS model) event fails, there is a loss of asymmetry or brain lateralization and the subsequent predisposition to schizophrenia and bipolar disorder. The genetic consequences do not show up as classical Mendelian mutations, and therefore (according to Klar) should be rather referred to as 'Mitogenetic' (see figure 1).

To test his hypothesis, Klar has used data from a large Scottish family with multiple members affected with both schizophrenia and bipolar disorder. The family was shown to have a translocation between chromosomes 1 and 11 that cosegregated with the disease phenotype. The family represents one of the best pieces of evidence arguing for a genetic role in development of these diseases because all individuals with the disease had the translocation. However, surprisingly, only 18 (nine schizophrenics and nine bipolars) among 36 translocation heterozygote individuals (i.e. 50%) are affected! Why is the translocation dominant in one half and recessive in the other half of carriers? Is it a simple case of 50% penetrance? Surprisingly, other studies involving

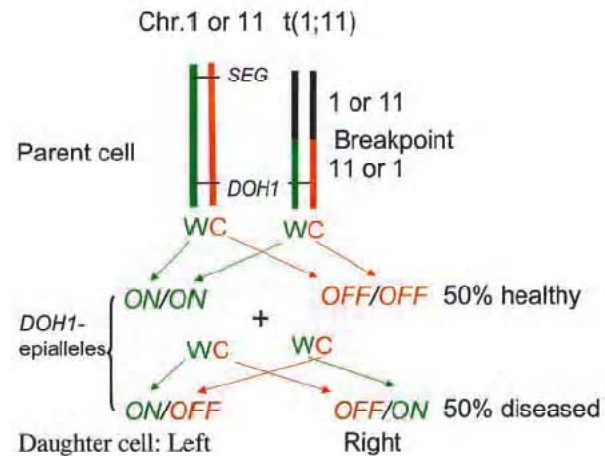


Figure 2. A genetic prediction of the SSIS model. (Reproduced from, A genetic mechanism implicates chromosome 11 in schizophrenia and bipolar diseases. Klar A. J. 2004 *Genetics*. **167**, 1833-1840.)

chromosome 11 translocations [t(6,11) and t(9,11)] (Holland and Gosden, 1990; Baysal *et al.* 1998) that relate also to psychosis revealed that exactly one-half of heterozygous translocation carriers get the disease and the other half are healthy. Then it looks highly unlikely that a single dominant modifier exists in heterozygous condition in all these three very different translocation-families resulting in 50% penetrance (see figure 2).

Chromosome 11 pair (or Chromosome 1 pair) (WC & W'C') may carry a hypothetical *DOH1* gene that is transcriptionally active (ON) in one specific parental strand (say W strand) and not on the other. Such a chromosome pair, following a non random segregation of the type described above, will give rise to ON/ON and OFF/OFF daughter cells. If the same chromosome also carries the genetic locus that actually controls the patterned non random segregation (*SEG*) of this chromosome pair, a translocation event that separates *DOH1* from *SEG* on one of the two chromosomes (heterozygote carrier) leads to the following genetic consequence. While the strands of the normal (not involved in translocation) chromosome are segregated to daughter cells in a patterned (non random) manner, those of the translocation carrying chromosome (due to the absence of *SEG* locus) segregate randomly to the daughter cells. Consequently, both daughters in one-half of the mitoses will have ON/ON plus OFF/OFF combination and the other half ON/OFF plus OFF/ON combination. If the former represents 'healthy' combination and the latter 'diseased', then this model best explains the puzzling data of why exactly 50% of heterozygous translocation carriers get the disease and the other half remain healthy. This is a simple model that invokes two genetic loci on the disease-relevant chromosome pair, where a translocation event between them on one chromosome randomizes the otherwise patterned segregation of epialleles, thereby yielding an equal fraction of

diseased to healthy carriers in a population.

The most important tenet of the model related to non-random strand segregation of WC and W'C' strands following mitosis received a good confirmation in a recent study of Cre-loxP-induced mitotic recombinants in mouse embryonic stem cells, where the genetic outcome of the distal markers, following a crossover event, was indicative of a highly efficient patterned segregation of chromatids such that all recombinants were homozygous (Liu *et al.* 2002).

Does Klar's model indeed explain the findings from the large Scottish pedigree with schizophrenia and bipolar disorder. Further investigation of the family members has suggested that ~70% of the translocation carriers may exhibit the disease phenotype, a finding that differs from Klar's prediction that only 50% of translocation carriers would be affected. The authors of that study also point out that the translocation disrupts two genes, *DISC1* and *DISC2* (disrupted in schizophrenia 1 and disrupted in schizophrenia 2) which may play a role in disease causation (Millar *et al.* 2003). However, the presence of other Chromosome 11 translocations associated with disease may suggest that either other genes or other models, like the one invoked by Klar also play a role. It is also possible that mutations in genes may act together with epigenetic mechanisms to produce the disease phenotype. Further study is required to test the validity of the SSIS model in a larger data set of patient families. The Klar model provides a novel and elegant way of invoking epigenetic mechanisms to explain the inherit-

ance of bipolar disorder and schizophrenia. It adds another level of complexity—or perhaps simplifies (!)—the genetics of complex psychiatric disorders and opens up new ways of looking at disease mechanisms.

References

- Baysal BE, Potkin SG, Farr JE, Higgins MJ, Korcz J, Gollin SM, James MR, Evans GA, Richard CW. 1998 Bipolar affective disorder partially cosegregates with a balanced t(9;11)(p24;q23.1) chromosomal translocation in a small pedigree. *Am. J. Med. Genet.* **81**, 81–91.
- Evans KL, Muir WJ, Blackwood DH, Porteous DJ. 2001 Nuts and bolts of psychiatric genetics: building on the Human Genome Project. *Trends Genet.* **17**, 35–40.
- Holland T. and C. Gosden. 1990 A balanced chromosomal translocation partially co-segregating with psychotic illness in a family. *Psychiatry Res.* **32**, 1–8.
- Klar AJ. 1987 Differentiated parental DNA strands confer developmental asymmetry on daughter cells in fission yeast. *Nature.* **326**, 466–470.
- Amar J. S. Klar. 2003 Response to Millar *et al.* Critique of Chromosome 1;11 Translocation Causing Psychosis. *Genetics* **163**, 837–838.
- J. Millar K., Thomson. P.A., Wray. N.R., Muir. W.J., Blackwood. D.H.R., and Porteous. D.J. 2003 Response to Amar J. Klar: the chromosome 1;11 translocation provides the best evidence supporting genetic etiology for schizophrenia and bipolar affective disorders. *Genetics*, **163**, 833–835.
- Liu, P., Jenkins N. A. and Copeland N. G. 2002 Efficient Cre-loxP-induced mitotic recombination in mouse embryonic stem cells. *Nat. Genet.* **30**, 66–72.