Perspectives

A proposal for re-defining the way the aetiology of schizophrenia and bipolar human psychiatric diseases is investigated

AMAR J S KLAR

Developmental Genetics Section, Gene Regulation and Chromosome Biology Laboratory, NCI-Frederick, MD 21702-1021, USA

(Fax # 301-846-6911; Email, klara@mail.nih.gov)

"The two big problems – the nature of development and the nature of the mind – are being subdued. I don't know whether there will be beautiful, general theories to come out of this – something really nice like Watson and Crick's double helix – or whether there will be an accumulation of more and more details. I'll confess to a secret hope for the former" (Crow 2000).

[Klar A J S 2010 A proposal for re-defining the way the aetiology of schizophrenia and bipolar human psychiatric diseases is investigated; *J. Biosci.* **35** 11–15] **DOI** 10.1007/s12038-010-0002-x

1. The causes of psychoses are unknown

Schizophrenia and bipolar affective human disorders are common human psychiatric diseases, each affecting about 1% of the population worldwide. Schizophrenia patients experience imaginary voices and visions, disorganized thought, and delusions. Bipolar or manic-depressive disorder causes periods of profound depression alternating with periods of excessively elevated mood swings called mania. Both disorders are thought to be mental disorders with overlapping symptoms and with common causes. The causes remain undefined despite decades of extensive research.

Recently published reviews summarized a lack of progress in identifying psychosis-causing gene mutations (Abbot 2008; Manolio *et al*. 2009). Manolio *et al.* (2009) reviewed the results of several hundred genome-wide association studies of so-called "complex diseases," and a large number of them concern schizophrenia and bipolar disorders. Numerous families and twin studies have been interpreted to indicate a genetic aetiology, but for psychoses the precise mode of inheritance has not conformed to the Mendelian genetics model. The molecular association studies have suggested numerous potential susceptibility loci spread over many human chromosomes, but studies investigating different affected families have failed to identify the relevant genes, even when data from multiple studies are pooled together (Lewis *et al.* 2003; Segurado *et al.* 2003).

Despite the clear lack of success in gene identification, the consensus is that a large number of genes with small effects, combined with environmental factors, is responsible for the disease aetiology. Such a description is routinely used to define complex diseases, but this consensus lacks experimental support for psychoses. The term "complex" implies common multifactorial traits; however, their causes remain unknown. As the conventional approaches of identifying disease-causing genes have failed, questioning basic assumptions of the field is justified, and if possible, a new paradigm for guiding psychoses studies should be contemplated.

2. Chromosome 11 translocations implicated in the disease

Is there another way to explain the aetiology of psychoses? Lacking identification of gene(s), what is the best evidence, if any, supporting a genetic aetiology? By far the most convincing evidence is that of chromosome (Chr.) 1;11 balanced translocation (figure 1). This translocation was proposed by workers in the field to implicate *DISC1* and

Keywords. Complex trait aetiology; developmental brain disorders; schizophrenia and bipolar diseases; selective chromatid segregation

2 (disrupted in schizophrenia) genes of Chr. 1 that lie at the translocation breakpoint (Evans *et al.* 2001). A major difficulty with the *DISC* genes proposition is that the *DISC* region did not show up in numerous other screens for psychosis genes. So, how can translocation cause disease? Likewise, two other translocations of Chr. 11, one with Chr. 6 and another with Chr. 9, cause disease in about one-half of heterozygous translocation carriers (figure1). The

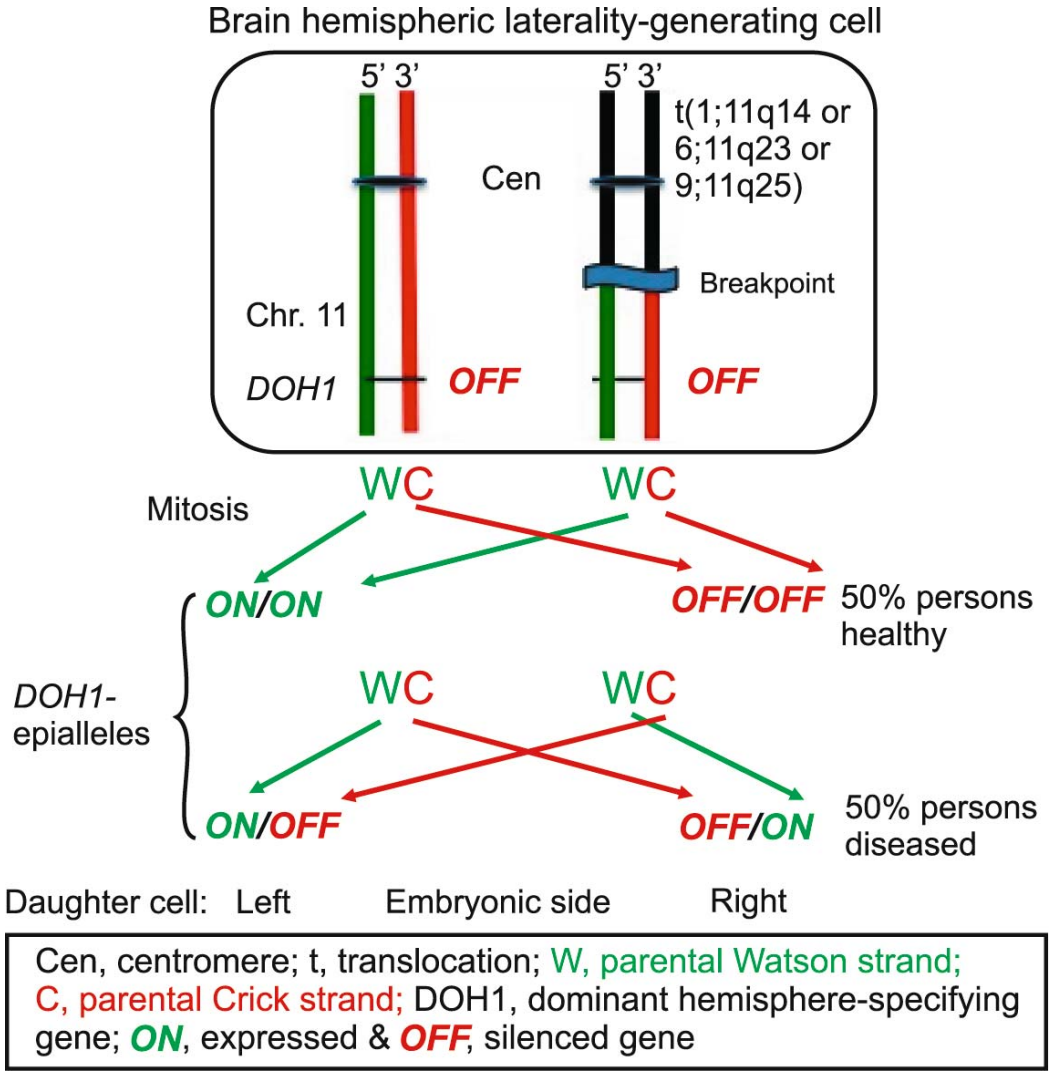

Figure 1. The SSIS model predicts 50% psychoses disease incidence in heterozygous Chr. 11 translocation carriers. The model is proposed as a mechanism for brain hemispheric laterality specification by Chr. 11 sister chromatids differentiation, through epigenetics, and their selective segregation, through centromeres, to affect an asymmetric cell division. Accordingly, the hypothetical brain-laterality determining *DOH1* gene is expressed ("*ON* epiallele") in the chromatid that inherits parental template, arbitrarily named "Watson" (W) strand defined by it's 5`-3` orientation, while it remains epigenetically silenced (*OFF* epiallele) in the sister chromatid inheriting the complementary template "Crick" (C) strand. This occurs during division of a brain laterality-generating progenitor cell early during embryogenesis. Only the epiallelic constitution of daughter cells is presented. By theory, sister chromatids of translocation-containing chromosomes are randomly segregated. Thus, precisely one-half of the translocation heterozygote embryos will produce both epigenetically equivalent (*ON/OFF*) daughter cells, resulting in developing psychoses later in life. For simplicity, the DNA chains are drawn as strait lines. The parental Chr. 11 W strands in the progenitor cell are coloured in green and parental C in red. The colour-coded arrows reflect segregation of colour-matched-strand-containing chromatids, bearing indicated *DOH1* epialleles, to specific daughter cells, one placed on the left and the other on the right side of the embryo.

breakpoints in these translocations span about 40% of the long arm of Chr. 11; therefore, it is highly unlikely a single gene is disrupted by three unrelated translocations (Klar 2004). How can the very distant translocation breakpoints be reconciled? Furthermore, why are only one-half of the heterozygous translocation carriers diseased in each family? Both schizophrenia and bipolar cases are found in translocation carrying families suggesting shared disease aetiology.

3. An epigenetic, chromosomal hypothesis for brain hemispheric laterality development

An epigenetic hypothesis neatly explains the genetic behaviour of translocations. It proposes *S*omatic DNA *S*trand-specific epigenetic *I*mprinting to cause silencing of a hypothetical *DO*minant brain *H*emisphere-specifying (*DOH1*) gene only in one of the two Chr. 11 sister chromatids on the basis of inheriting 'Watson' versus 'Crick' DNA template strand sequences, coupled with selective chromatid *S*egregation of epigenetically differentiated chromatids to specific daughter cells (the *SSIS* hypothesis, figure1) in the embryo. The theory was advanced as a general mechanism to produce asymmetric cell division by exploiting double helix structure of DNA (Watson and Crick 1953) and the strand-specific epigenetic gene regulation processes that might operate during specific cell division in embryogenesis. Accordingly, healthy brain hemispheric laterality development results from an asymmetric cell division specifically when initial hemispheric laterality of the brain is established in the embryo. By this hypothesis, translocation would cause random chromatid distribution of the Chr. 11 arm because of its association to a centromere that usually promotes random sister centromeres distribution. This randomness would compromise brain laterality development in only one-half of translocation heterozygous individuals to cause disease (Klar 2004; Singh and Klar 2007). A breakpoint of one of the translocations did not disrupt any gene and the usual explanation proposed by workers is that the breakpoint might affect expression of a nearby gene by "position effect". Also, there is a very low probability (approximately 0.000009) whereby three translocations would affect the same condition at random, with breaks located in the same chromosome arm at vastly different places. Translocations clearly implicate Chr. 11 for disease in these families but breakpoint regions in all cases have not been implicated in subsequent genetic screens. Overall, different translocations provide strong genetic evidence for psychoses aetiology and for the SSIS hypothesis. Novel interpretation should be emphasized here: disease develops because of mitotic genetics ("mitogenetics"; Klar 2008) chromatid segregation anomaly, but without any gene having been mutated in translocations.

The SSIS theory was first proposed as a mechanism for lateralization of visceral organs in the mouse (Klar 1994). Supporting this idea, chromosome-specific selective chromatid segregation has been recently discovered in mouse cells (Armakolas and Klar 2006). Moreover, the *Left-right dynein* gene has been implicated in the selective chromatid segregation process (Armakolas and Klar 2007; Klar 2008). Consistent with the asymmetric cell division postulate of the SSIS model, the chiral blastomere arrangement of the embryo specifically at the 8-cell stage determines the direction of the snail's left-right body asymmetry (Kuroda *et al.* 2009). In principle, asymmetric cell division might cause human brain hemispheric laterality specification, and psychoses may result when brain hemispheric laterality development is compromised.

4. Developmental noise proposed to cause disease

The new paradigm of the SSIS model does not necessarily mean that general cases of psychoses must also result from chromosome rearrangements. Most cases of psychoses are sporadic and, as stated above, are not associated with any known genetic cause(s). Since brain left/right hemispheric cognition specialization is partially associated with human right- versus left/ambidextrous hand-use preference and/or with clockwise versus anti-clockwise scalp hair-whorl orientation, genetics controlling lateralization of these embryonic ectoderm layer-derived traits should be considered as the major psychoses predisposing factor (Klar 2003, 2005; Schwarzburg 1927), but where only a fraction of such carriers develop disease. Because a vast majority of such genetically predisposed persons do not develop disease, gene(s) controlling handedness and/or hair-whorl orientation and psychoses traits will not have been identified in screens for psychosis-correlated genes. Moreover, general cases of psychoses might also result from spontaneous and random somatic Chr. 11 recombination events or other genetic mechanisms that disrupt imprinting or the biased chromatid segregation processes postulated in the SSIS hypothesis. In other words, a normally operating "developmental noise" affecting brain laterality development might be the predominant root cause in general cases of psychoses.

5. Arguments concerning the prevailing research viewpoint

This new paradigm necessitates reconsideration of the two main arguments of the psychiatric genetics field that have guided the prevailing paradigm of gene-finding studies: increased disease incidence runs in families, and when one monozygotic twin is diseased, up to 50% of co-twins are also affected (Manolio *et al.* 2009). Studying families with a high incidence of psychoses was initially well justified since

this approach has borne fruit for other complex diseases, such as diabetes, where mutations in multiple genes have been implicated (Manolio *et al.* 2009). However, having failed to implicate genes in families with a high incidence of psychoses, I suggest that the trait "running-in-families" is an invalid argument to be viewed presently as supportive of a genetic aetiology.

Clearly, the entire field fell prey to a circular argument of selection bias of researched families. Also, observations of monozygotic twins' concordance/discordance do not necessarily implicate either genetic or environmental factors, because the biology of twinning might cause diseases in ways not applicable to single births. For instance, both in humans and amphibia, one member of a conjoined pair joined at the stomach develops inverted visceral organs in 50% of cases (Aw and Levin 2009). In contrast, in the general public only 1 in 10,000 humans develop this anomaly. Let us designate it as a "phenocopy-effect" and it might result from developmental errors caused by the embryo-splitting process occurring during twinning. For example, the *Left-right dynein* gene that controls visceral laterality arrangement in the mouse is silent in some cell types and expressed in others (Armakolas and Klar 2007). In principle, such developmentally regulated gene silencing might have already occurred for the gene before embryo splitting to cause random visceral laterality in one of the twin members. Similarly, the twinning process itself might cause a developmental disorder in brain laterality establishment.

6. Conclusions and future research

The prevailing approach of the field consists of recruiting a much larger number of families and subjecting them to genome-wide association studies to identify genes with small effects. This approach continues to be an expensive endeavour. In light of not finding disease-causing mutations employing this approach following extremely extensive research conducted thus far, the basic tenets of the prevailing paradigm are questioned and a discussion is presented for an alternative theory in this perspective. It is argued here that most cases of psychoses are neither due to environmental stress, nor due to specific gene mutations. Rather, genetically predisposing factors and spontaneous events are proposed to interfere with functioning of the SSIS processes. Such developmental noise is proposed to interfere with brain laterality development to cause brain disorders. Similar developmental noise independently might affect our visceral organs' laterality development, but such cases might be lost due to embryonic lethality (Klar 2008). On the other hand, brain laterality anomalies might not cause embryonic lethality, resulting in psychosis cases. Future studies should scrutinize this alternative hypothesis that posits strictly epigenetic gene regulation mechanisms for brain and visceral organs' laterality development and for disease causation. Of note, defining disease cause is urgently needed before rational disease intervention can be envisaged. Last, potentially fulfilling the wishes of Crow quoted above, the SSIS model builds on the double helix structure of DNA to provide us with a chromosome-based epigenetic mechanism for development.

Acknowledgements

The Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research at Frederick, Maryland, USA, has supported this research.

References

Abbot A 2008 The brains of the family: Does the difficulty in finding the genes responsible for mental illness reflect the complexity of the genetics or the poor definition of psychiatric disorders?; *Nature (London)* **454** 155–157

Armakolas A and Klar A J S 2006 Cell type regulates selective segregation of mouse chromosome 7 DNA strands in mitosis; *Science* **311** 1146–1149

Armakolas A and Klar A J S 2007 Left-right dynein motor implicated in selective chromatid segregation in mouse cells; *Science* **315** 100–101

Aw S and Levin M 2009 Is left-right asymmetry a form of planar cell polarity?; *Development* **136** 355–366

Crow J F 2000 Two centuries of genetics: a view from halftime; *Annu. Rev. Genom. Hum. Genet.* **1** 21–40

Evans K L, Muir W J, Blackwood D H and Porteous D J 2001 Nuts and bolts of psychiatric genetics: building on the Human Genome Project; *Trends Genet.* **17** 35–40

Klar A J S 1994 A model for specification of the left-right axis in vertebrates; *Trends Genet.* **10** 392–396

Klar A J S 2003 Human handedness and scalp hair-whorl direction develop from a common genetic mechanism; *Genetics* **165** 269–276

Klar A J S 2004 A genetic mechanism implicates chromosome 11 in schizophrenia and bipolar diseases; *Genetics* **167** 1833–1840

Klar A J S 2005 A 1927 study supports a current genetic model for inheritance of human scalp hair-whorl orientation and hand-use preference traits; *Genetics* **170** 2027–2030

Klar A J S 2008 Support for the selective chromatid segregation hypothesis advanced for the mechanism of left-right body axis development in mice; *Breast Dis*. **29** 47–56

Kuroda R, Endo B, Abe M and Shimizu M 2009 Chiral blastomere arrangement dictates zygotic lef-right asymmetry pathway in snails; *Nature (London)* **462** 790–794

Lewis C M, Levinson D F, Wise L H, DeLisi L E, Straub R E, Hovatta I, Williams N M, Schwab S G *et al.* 2003 Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia; *Am. J. Hum. Genet*. **73** 34–48

Manolio T A, Collins F S, Cox N J, Goldstein D B, Hindorff L A, Hunter D J, McCarthy M I, Ramos E M *et al.* 2009 Finding the

missing heritability of complex diseases; *Nature (London)* **461** 747–753

Schwarzburg V W 1927 Statistische untersuchungen uber den menschlichen scheitelwirbel und seine vererbung; *Z. Morphol. Anthropol*. **26** 195–223

Segurado R, Detera-Wadleigh S D, Levinson D F, Lewis C M, Gill M, Nurnberger J I Jr, Craddock N, DePaulo J R *et al.* 2003 Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder; *Am. J. Hum. Genet.* **73** 49–62

Singh G and Klar A J S 2007 A hypothesis for how chromosome 11 translocations cause psychiatric disorders; *Genetics* **177** 1259–1262

Watson J D and Crick F H 1953 Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid; *Nature (London)* **171** 737–738

*e*Publication: 3 February 2010