

Appendix A14.4

The Utility of Endophenotypic Strategies in Bipolar Disorder

It is clear that bipolar disorder arises from the interaction of multiple susceptibility (and likely risk) genes. These genes (and the proteins they code for) are undoubtedly related to specific biochemical processes and thus specific symptoms, rather than the rigid *DSM-IV* diagnostic criteria of bipolar disorder.

One strategy which may have considerable utility in elucidating the complex neurobiology of bipolar disorder is an endophenotype-based approach (Lander, 1988; Gould and Manji, 2002). Such an approach may also be useful for the enrichment of study populations based on pathophysiological considerations, and may ultimately lead to a greater understanding of the illness. For example, certain abnormal neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, and neuropsychological effects are often found to accompany psychiatric illness. In many cases these effects produce no overt clinical signs and symptoms (i.e. exophenotypes), thus requiring a specific assay or procedure to ascertain their presence. Some of these findings may eventually be useful in sub-defining complex genetic disorders, thereafter allowing for improvements in diagnostic assessment, genetic linkage studies, and the development of animal models. The term *endophenotype* (also referred to as biological marker, subclinical trait, and vulnerability marker) is often used to describe these traits (Gottesman and Shields, 1972). In 1986 Gershon and Goldin described four criteria useful for the identification of markers (endophenotypes) in complex genetics (Gershon and Goldin, 1986):

1. Marker is associated with illness in the population
2. Marker is heritable
3. Marker is state-independent (manifests in an individual whether or not illness is active)
4. Within families, marker and illness co-segregate

Subsequently, an additional criterion was suggested that may be useful for identifying endophenotypes of diseases that display complex inheritance patterns (Leboyer et al., 1998):

5. Markers are found in non-affected family members at a higher rate than in the general population

Theories of complex genetics predict that these endophenotypes will have simpler genetic underpinnings and be more common in the population than the disorder itself, allowing for simpler and more straightforward linkage analysis (Leboyer et al., 1998). Furthermore,

identification of endophenotypes through candidate symptoms among affected subjects and recognition of sub-clinical traits among non-affected relatives may provide more accurate chromosomal localization of a subset of genes that underlie a complex disorder.

This endophenotype strategy has been successful in locating genes that cause non-psychiatric disorders, such as the multiple genes that cause long-QT syndrome, which were identified using an endophenotype-based method (Keating et al., 1991; Keating and Sanguinetti, 2001). Manifestations of long-QT syndrome include syncope, ventricle arrhythmias, and sudden death (Keating and Sanguinetti, 2001). While not all family members who carry the disease genes show these symptoms, electrocardiogram shows a much greater percentage of QT elongation than in the general population, thus allowing for successful genetic linkage studies (Keating et al., 1991; Vincent et al., 1992).

In psychiatry this approach may be equally useful once reproducible endophenotypes have been identified. Indeed the use of an endophenotype approach has already had some success in psychiatry. For example, Freedman and colleagues used an endophenotype found in both probands and non-affected relatives of patients with schizophrenia—abnormal P50 auditory evoked potentials—to identify a potential susceptibility loci for this disease on chromosome 15 (Freedman et al., 1997). More recently, Egan and colleagues associated performance on a working memory task in patients with a specific allele variation of catechol-O-methyltransferase. Changes in working memory performance were found in patients with schizophrenia and in their unaffected siblings to be associated with this allele variation (Egan et al., 2001).

Similarly to the objective manner in which endophenotypes can be monitored in patients, physiological and neurobiological signs can also be measured in animals harboring either naturally occurring or experimentally-induced anomalies in evolutionarily conserved behaviors. Many features of a major psychiatric illness like bipolar disorder (euphoria, racing thoughts, depressed mood, guilty ruminations, and suicidal thoughts) can only be fully appreciated in humans wherein the cortical mantle has evolved to a greater extent than in other species. On the other hand, many endophenotypes of bipolar disorder have their counterparts in non-human mammalian species, such as the mouse, thus potentially allowing for phenotypes that can be modeled in the laboratory. Neurobiological characteristics of depression and mania that may occur as the result of single gene effects include abnormalities in hypothalamic regulation of sleep/autonomic/hormonal physiology, altered appetite and libido, altered sleep-wake cycles, and psychomotor activity.

Conceptualizing these diseases using an endophenotypic approach may also allow for a more biologically relevant classification of patients along dimensional properties of the disorder, rather than the traditional categorical classifications imposed by our diagnostic manuals and reimbursement systems. In the absence of the full phenotypic expression of complex behavioral disorders in non-human species, the identification of susceptibility loci and, ultimately, candidate

genes for bipolar disorder, will permit the creation of animal models with construct validity based upon the endophenotype of interest.

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