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New Linkage Findings in Affective Disorders*

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Summary. Identification of single-gene forms of manic-depressive illness, through linkage demonstrations in pedigrees, offers important opportunities for identification of pathophysiological mechanisms, and for genetic counseling in families with a valid marker of vulnerability.

Key words: Genetic linkage – Chromosomal Markers – X-chromosome – Chromosome 11 – DNA – Restriction fragment length polymorphism

In a time of very rapid progress in molecular genetics, the psychiatric investigator cannot be satisfied with analyses of inheritance which offer statistical regression explanations of diagnostic correlations between relatives, even when they satisfactorily predict observed prevalences, because such interpretations do not lead to the discovery of a specific biological component of the diagnostic correlation, such as a specific gene. If a specific gene is discovered, on the other hand, its location, sequence, and function can then yield further understanding of the phenomenon studied. Thus, in all fields of medicine, the distinction between multifactorial and single-locus inheritance has become crucial to scientific progress in understanding many common diseases with complex inheritance, among them the major psychiatric disorders.

For the past several decades these disorders have been thought of by psychiatrists as multifactorial in their transmission, by which was meant that each disorder resulted from a cumulative effect of numerous hypothesized developmental events, social and cultural environmental events, and genetic contributions (Gottesman and Shields 1982). The acceptance of a genetic component is historically related to the published findings in the mid-1960s of Heston, and of Kety, Rosenthal, Wender, Schulsinger, and their colleagues (Heston 1966; Kety et al. 1968, 1975; Rosenthal et al. 1968), who demonstrated that schizophrenia and related disorders were found in excess in the biological relatives of adopted schizophrenics. Since the adoptions had occurred early in infancy, there was a strong implication that the transmission was genetic, although prenatal and perinatal events might still be considered as causes. In combination with 50 years of evidence from twin and family studies pointing to the same conclusion in schizophrenia and in the major affective disorders, genetics was gradually accepted as one among many factors which could predispose a person to certain emotional disorders.

The recent demonstrations that there exists single major locus inheritance of manic depressive illness, through linkage marker studies of pedigrees reviewed here, must radically change this perspective. A linkage demonstration provides strong evidence that a single genetic event exists which has profound influence on a complex set of human behaviors, and that this event can, with very high probability, be said to be present in particular individuals and absent in others. In this era of advances in molecular genetics, the linkage findings provide a reasonable expectation that the biological nature of the event is discoverable with current research methods.

Identification and characterization of single locus events has become the premier current challenge of genetic research in psychiatry, rather than settling the less tangible question of whether or not inheritance is playing a role in the major psychiatric disor-

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ders. In the affective disorders, the recent reports of linkage on chromosome 11 and on the X-chromosome have aroused the greatest interest, and they are reviewed here.

Single locus methods are not the only way to investigate inherited biological vulnerability in psychiatric disorders, of course. Model-free methods have also been developed to study inheritance of putative illness-causing biological traits, in which a characteristic is shown to be inherited by concordance in twin or family studies, and it is demonstrated to be more likely found in ill persons or in persons at risk of illness than in controls (Rieder and Gershon 1978; Gershon and Goldin 1986; Sitaram et al. 1988). There are some promising biological phenomena which are associated with inheritance of illness by these methods (DeLisi et al. 1986; Goldin et al. 1986), which are reviewed elsewhere (Goldin and Gershon 1988; Goldin et al. 1987).

Chromosome 11. The use of very large pedigrees in linkage studies is based on the assumption that even in an illness that is genetically heterogeneous, there will be genetic homogeneity within pedigrees. This is questionable for a common disease in a large population, where persons marrying into the pedigree may bring in different forms of illness, but in a population isolate homogeneity may be considered more likely, at least within a pedigree. The Amish population studied by Egeland is an isolate in which several large pedigrees segregating for affective illness have been identified. In one pedigree, Egeland et al. (1987) found autosomal dominant transmission and linkage of bipolar and unipolar illness to the Insulin-ras oncogene region of the short arm of chromosome 11. In Bethesda, Maryland, we (Detera-Wadleigh et al. 1987) have found this linkage not to be present in three smaller pedigrees, and Hodgkinson et al. (1987), in three Icelandic pedigrees, also did not find this linkage. It is difficult to find methodological fault with the Amish study, since the pedigrees were cultured, with the diagnoses and cells available to interested scientists, before the chromosome 11 markers were applied to it. The non-replication seems to be due to genetic heterogeneity in this case, with the implication that the Amish form of manic-depressive illness is genetically uncommon in the other populations studied.

X-chromosome. Between 1969 and 1974, Winokur and his colleagues (Reich et al. 1969) and shortly afterwards Mendlewicz and co-workers (Mendelewicz and Fleiss 1974; Mendelewicz et al. 1972, 1975) reported that biplar illness is linked to the X-chromosome markers Xg blood group and Protan/Deutan color blindness. At the time of the initial reports, it was not known that these results were inconsistent with each other, because linkage of bipolar illness to both Xg and to protan and deutan color blindness is not compatible with the known large chromosomal map distance between the Xg locus (on the short arm) and the protan-deutan region (at the tip of the long arm).

We were unable to replicate either of these linkages in our own data. For both Xg and protan-deutan color blindness, close linkage to affective illness was ruled out (Leckman et al. 1979; Gershon et al. 1979). Our pedigrees were not heterogeneous with respect to each other and there were no single pedigrees strongly suggesting linkage to either marker. Mendlewicz and associates (1979), on the other hand, reported eight new families in Belgium and suggested linkage to color blindness in at least one.

It has been argued (Risch and Baron 1982) that there is linkage to color blindness but not Xg blood group, and that heterogeneity accounts for differences between investigators. This is difficult to accept when the initial series was so strikingly positive and the replication series so negative, and also in view of the inconsistency of the initial finding that both Xg and color blindness were linked to bipolar illness. If methodological errors in diagnostic or ascertainment procedures produced the unique homogeneity of the 1972–1974 pedigree series of Mendlewicz and colleagues, that would explain why the strikingly positive results are not replicated either in our series or in the later series of Mendlewicz et al. (1979).

Strongly positive, multigenerational, pedigrees for the red-green color blindness linkage have since been reported by Baron and co-workers (see summary in 1987 publication) and Mendlewicz and coworkers have reported linkage to the glucose-6-phosphate dehydrogenase (G6PD) locus (a marker on the X-chromosome very close to the red-green color blindness loci) (Mendlewicz et al. 1980) and to the blood clotting factor IX, which is within 15–30 centimorgans of the red-green color blindness region (Mendlewicz et al. 1987).

Since DNA probes for this region of the X-chromosome now exist, their use may make virtually all pedigrees informative for linkage and lead to a resolution of the controversy of whether or not there is a generally reproducible finding of linkage to the color blindness region in a portion of manic depressives. My colleagues Berrettini, Gelernter and Detera-Wadleigh, and I have recently applied the St14 probe of Oberle et al. (1985), which marks the color blindness of the X-chromosome, to new manic-depressive pedigrees, and continue to find linkage to be excluded (Gelernter et al. 1987).

Although the RFLP data described in this paper apply only to the 11p and Xq28 chromosomal regions, there is now an almost complete human gene mapping capacity, using RFLPs (Donis-Keller et al. 1987). The question of whether there are single major loci of importance in the inheritance of the major psychiatric disorders is therefore solvable be currently envisagable methods, applied to numerous psychiatric pedigrees. It appears important to settle this issue. If there is a single locus form in a disorder such as schizophrenia, it would allow for clinical prevention strategies based on early identification of persons at high risk, and offer information for genetic counseling when it is sought. More importantly, it would offer important clues on what is the gene defect associated with (and perhaps crucial in causation of) the illness. If there is not a single locus linked to illness, this would force investigative attention onto multifactorial etiologies. In biological investigation, one would concentrate on metric characteristics inherited in polygenic fashion, including various cognitive abilities and measures of cerebral anatomy and metabolism.

In the pursuit of a valid linkage marker, can we determine a priori which markers to study in which illness? Of course, this does not matter in the long run, since if there is linkage the same chromosome fragment will be identified by random single copy markers or by markers derived from genes important in neuronal function. Nonetheless, it appears important to study genes about which some biological hypothesis can be offered that is worth testing in the linkage study, since such a study adds the possibility of directly specifying the gene defect in the illness. The next step after establishing linkage, to search the specified chromosomal region for the gene variant producing illness, may prove more arduous than finding the linkage (Little 1986).

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