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Genetic epidemiologic studies of affective disorders in childhood and adolescence

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Summary. The application of the methods of genetic epidemiology appears to be one of the most promising avenues to unravel the complex mechanisms through which genes may exert their influence. The approaches of genetic epidemiology are particularly important for those diseases which are characterized by moderate degrees of heritability and lack of direct correspondence between the underlying vulnerability factors and the ultimate expression of the disease, as is the case for affective disorders. The application of the methods of genetic epidemiology to children of affected parents may also elucidate environmental risk factors and early signs of the disorder. Perhaps the most important implication of the identification of genetic markers for affective disorders is the opportunity for prevention of the disorders. Early identification of youngsters who do manifest early signs of the disorders would facilitate secondary and tertiary prevention of the consequences of those conditions.

Introduction

Rapid developments in molecular biology have introduced a new era in human genetics. Although only a decade ago linkage depended upon inferences about the underlying genetic polymorphic DNA markers, the methods for processing and sequencing the DNA have dramatically enhanced our ability to detect linkage between these markers and diseases for which no aberrant gene product has been identified. Family pedigrees may be examined to determine whether a particular disease or trait is associated with a specific DNA marker (i.e., linkage). Since the exciting discovery of a linked marker for Huntington's disease in 1983 (Gusella et al. 1982), numerous other diseases have followed, and the primary gene defect has now been discovered for Duchenne-type muscular dystrophy (Kunkel et al. 1986) and cystic fibrosis (Beaudet et al. 1986).

Despite this dramatic success, the application of these methods to psychiatric disorders has been quite disappointing. The initial report of linkage between affective disorders and DNA markers on chromosome 11 (Egeland et al. 1987) was followed 2 years later by disconfirmation of the finding, in a larger sample from the same pedigree (Kelsoe et al. 1989). More recently, Baron et al. (1993) published the results of their failure to confirm their previous report of X-linkage to bipolar disorder in Israeli pedigrees based on phenotypic expression of X-chromosome markers, with direct analysis of the DNA polymorphisms.

The lack of conclusive evidence regarding the role of genes in the etiology of affective disorders may be attributed to a number of characteristics that impede genetic studies of this condition. The major psychiatric disorders, and the affective disorders in particular, constitute complex human disorders, characterized by: lack of clear separation between affected and unaffected status; a high population prevalence such that clustering of affected patients in some families may occur by chance even if not genetic; an unspecific etiology and pathophysiology underlying a complex set of symptoms that are common to a number of different causes, and failure to adhere to Mendelian patterns of transmission. That is, the relative risk of affective disorders is significantly different from the value 2 for concordance rate among monozygotic versus dizygotic twins, and for risk of disorder among first-degree versus second-degree relatives. Moreover, adoption studies have revealed strong environmental influences on the etiology of depression (Cadoret et al. 1985). Epidemiologic studies have yielded estimates of the lifetime prevalence of all affective disorders ranging from 5 to 25%, and of bipolar subtype of 0.5–2%. There has been a large number of family studies of the affective disorders; however, there are only a limited number that provide information on the recurrence risk among relatives beyond the first degree. The average risk of bipolar disorder among first-degree relatives of bipolar probands is approximately 8%, with variability according to the definitions of bipolar disorder.

Despite the strong evidence for familial aggregation of the affective disorders, the heritability of the major subtypes has not been well-established. Numerous fam-

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Table 1. Impediments to genetic studies of affective disorders

> Complex disorder
> Validity of diagnostic criteria
> Comorbidity with other disorders
> Non-random mating
> Secular trends

ily studies have established the familial nature of several syndromes; however, they cannot ascribe relative weights to genetic and environmental influences, nor discriminate between genetic and non-genetic factors that may account for some of the patterns of illness found in pedigrees.

There are a limited number of twin and adoption studies that have examined the role of genetic factors separately from environmental influences in the etiology of affective disorders according to subtypes. The twin studies have yielded evidence for a high degree of heritability of bipolar disorder (Bertelsen et al. 1977; Mendlewicz and Ranier 1977). Wender et al. (1986) demonstrated an eightfold increase in unipolar depression among the biological relatives of adoptees with mood disorders compared to control adoptees, while milder depressive syndromes showed considerably less genetic determination.

Linkage studies of complex human disorders must be designed with careful consideration and interpretation of the information that has been gleaned from epidemiologic and family studies of that disorder. The family, twin, and adoption studies suggest a high level of heritability of bipolar disorder, but fail to establish a single mode of transmission. The lack of well-defined Mendelian patterns of inheritance (i.e.,single major locus, autosomal or X-linked, dominant or recessive) has been a major impediment to linkage studies of bipolar disorder. This underscores the need for more family, twin and adoption studies capable of examining the transmissibility, heritability, and role of environmental factors in the subtypes of the affective disorders. Some of the major impediments to genetic studies of affective disorders are shown in Table 1.

Methods of genetic epidemiology

The application of the methods of genetic epidemiology, a science that studies patterns of familial aggregation of diseases in the general population, appears to be one of the most promising avenues to unravel the complex mechanisms through which genes may exert their influence. The approaches of genetic epidemiology are particularly important for those diseases which are characterized by moderate degrees of heritability and lack of direct correspondence between the underlying vulnerability factors and the ultimate expression of the disease.

Examples of a lack of one-to-one correspondence between the genotype and phenotype are as follows: genetic heterogeneity (multiple genetic mechanisms evoking the same or clinically indistinguishable phenotype); epistasis (interaction between several distinct genes); phenotypic heterogeneity (variability in the clinical expression of the same genes); phenocopies (manifestation of a disease in the absence of the underlying genetic factors, or false-positives); and gene-environment interaction (specific environmental context required for gened expression).

The two chief study paradigms for studying gene-environment interactions involve holding either the genetic background or the environment constant and evaluating systematic changes in the other (MacMahon 1968; Susser 1985). Examples of studies that hold genetic background constant while observing differential environmental exposures include: studies of discordant twins, migrant population studies, relatives exposed to a particular agent such as a virus, twins reared separately, or the family set design, in which comparisons are made among families of similar structure living in distinct environments.

Examples of paradigms in which the environment is held constant while genetic factors are allowed to vary include: monozygotic twins of affected individuals compared to dizygotic twins and non-twin siblings; offspring of consanguineous matings, compared to those of non-consanguineous matings; half siblings compared to full siblings living in the same home; and first-degree relatives of affected individuals. In both types of studies, observations can be made regarding time-space clustering of disease, usually attributable to environmental agents, or a characteristic age of onset and course, that are primarily due to genetic factors.

A basic approach of genetic epidemiology is the use of the within-family design to minimize the probability of heterogeneity, assuming that the etiology of a disease is likely to be homotypic within families. This design reduces or eliminates the danger of genetic heterogeneity which is likely to characterize depression. Although all individuals within a particular sibship are not expected to share equal genetic risk because of independent segregation of genes, the same etiologic factors may be implicated when multiple siblings are affected.

After familial transmission of a disease has been established, the immediate goal of genetic epidemiologic studies is to identify the relative degree of phenotypic variance that can be attributed to genetic factors and transmissible and non-transmissible environmental factors. The ultimate purpose of such studies is to identify the specific agents that play an etiologic or contributing role to the development of the trait. The multifactorial model of disease transmission provides a convenient paradigm with which to investigate the role of familial transmission of the affective disorders. This model, first proposed by Falconer (1965), specifies that there are numerous genes and transmissible and non-transmissible cultural factors that are additively and independently (i.e., without epistasis) involved in producing a phenotype. There is assumed to be a continuous underlying distribution, or liability, which is defined as the propensity for expressing a disease. The total liability includes genetic (or transmitted) components and non-transmitted components of the variance. The liability is assumed to be normally distributed with mean = 0 and variance = 1. When a sufficient number of these factors is present, the individual will fall beyond the threshold, or the point on the distribution beyond which the disorder becomes manifest. (See Fig. 1)

This model is most appealing because it leads to discrimination between transmissible and non-transmissible risk factors, and, when combined with appropriate study designs, can also differentiate between shared genes and cultural, or non-genetic factors that tend

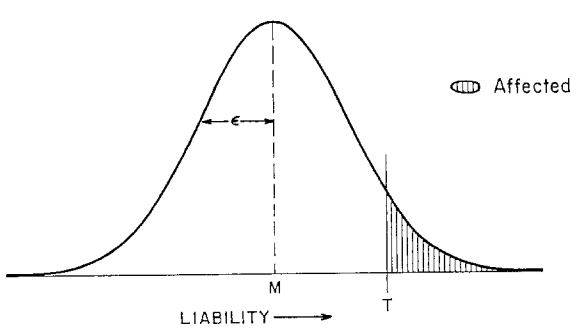

Fig. 1. Polygenic thresholds model of disease transmission. $M = 0$, $\varepsilon = 1$

to aggregate in families. Moreover, the use of a continuous rather than discrete model of measurement of affective disorder provides a more adequate representation of depression as an expression of an underlying continuum ranging from the expression of normal human emotion to severe depressive disorder. The risk factors for depression can be conceptualized according to each of the components of the model as described below.

Application to studies of affective disorders in children

Assessment of depression in children and adolescents

There is extensive literature regarding the measurement of depression in children and adolescents. Standardized assessments of adolescents range from self-report symptom checklists to highly structured diagnostic instruments. The advantages and disadvantages of each of these approaches have been summarized by Orvaschel (1985). In brief, the symptom checklists are dimensional, thereby avoiding arbitrary discrimination between affected and unaffected respondents; have well-established psychometric properties; and often have extensive normative data available. Disadvantages of such checklists include: a lack of specificity of high scores, partially attributable to lack of data on the context, frequency and severity of symptom expression; restricted time period of assessment, generally limited to the current data or past week; the generation of insufficient information with which to assess diagnotic criteria; and weak evidence on the criterion validity of such measures (Brunshaw and Szatmari, 1988).

In contrast, structured diagnostic interviews provide uniformity of data collection in the clinical interview setting, generate criteria to yield standardized diagnoses, assess the context, frequency, duration and impairment of symptom constellations, and generally provide the best approximation to the clinical interview. Weaknesses often include: a lack of flexibility in the use of clarification and symptom probes by the interviewer; the use of a flow chart format based on diagnostic thresholds, which precludes the collection of subthreshold data on symptoms, duration, frequency, or impairment; and the lack of clinical judgment on the part of the interviewer in interpreting the interview responses.

The use of structured diagnostic interviews in child psychiatry has evoked abundant research on the reliability of diagnoses in children and adolescents. Although the wide discrepancy between child and parent report has alarmed investigators in child psychiatry, the differences are often greater in family studies of adults. Most studies of adolescents employ the child him/herself as the major source of information, with ancillary information from parents being of secondary importance in rendering diagnostic information (Orvaschel et al. 1980).

Assessment of children in family studies

In addition to the traditional standards of family study methodology, there are several issues that should be considered in family studies which include children. Most important is the application of broad assessments of children, in whom the typical patterns of expression of adulthood depression have not yet crystallized. In addition to the use of structured diagnostic interviews to ascertain disorders defined according to the current diagnostic nomenclature, subthreshold definitions and dimensional assessments of the traits which underlie the disorders should be employed. Moreover, because of the magnitude of co-occurrence of affective disorders and other conditions in children, comorbidity should be systematically assessed.

Although it would be expected that children contribute little information to the estimates of recurrence risk in families due to the small proportion of the risk period that they have surpassed, the magnitude of the rates in the familiy studies below suggest that children in families of affected parents may have an earlier age of onset than would be expected from our limited knowledge of age of onset distributions derived from clinical and epidemiologic samples.

Family studies of offspring of parents with affective disorders

Despite the abundance of well-controlled family and genetic studies which have employed sophisticated methodology to investigate the transmission of affective disorders among adults, there are only a limited number of controlled family studies which have focused on the manifestation of affective disorders among adolescents. Reviews of early family studies of parents with affective illness have been presented by Beardslee et al. (1983), and more recent studies by LaRoche et al. (1987) and Downey and Coyne (1990). Methodologic limitations of these studies, including a lack of adequate comparison and control groups, absence of blindness to parental diagnostic status, biased samples of proband parents, and nonstandardized assessments of disorders in children, have been well-recognized and have improved substantially in recent studies. Nevertheless, integration of the findings across studies is still precluded by wide variation in the demographic and clinical features of the samples. Tables 2 and 3 present a summary of controlled studies of offspring of parents with bipolar and non-bipolar depression, respectively. The studies reviewed herein are limited to those in which offspring in the age range of adolescence were assessed.

The five controlled studies of offspring of parents with bipolar disorder exhibit wide variation in the magnitude of affective disorders among offspring of affected parents with a range of 26–67% (Table 2). Similar variation among the controls suggests major methodologic differences in the selection of probands and assessments across studies. The relative risk among children of the cases compared to those of control parents was elevated in four of the five studies. The most remarkable finding in these studies was the high rates of all psychiatric disorders, which exceeded 50% in most studies. The finding that the majority of disorders in these offspring were comprised of affective syndromes demonstrates some specificity of transmission of the affective disorders. However,

Table 2. Controlled studies of the offspring of parents with bipolar depression

Authors (Year)	Proband		Controls		Offspring				Disorders in offspring (rates/100)			
									Affective		Any DX	
	N	Source	*N*	Source	*N* Cases	*N* Controls	Age (years)	DX Interview	Cases	Controls	Cases	Controls
Decina et al. (1983)	18	Outpatient	14	Psych. outpatients	31	18	7–14	MHAF[a]	26	0	52	5
Klein and Depue (1985)	26	Inpatient	22	Psych. outpatients	41	22	15–21	SADS-L[b]	38	5	43	18
Gershon et al. (1985)	16	Inpatient Outpatient	19	Normal	29	37	6–17	K-SADS	41	38	72	51
Hammen et al. (1987)	9	Female Outpatient	14 22	a) Medically ill b) Normal	12	a) 18 b) 35	8–16	K-SADS	67	17	92	29
Nurnberger et al. (1988)	32	Inpatient	39	Volunteers	53	39	15–25	SADS-L[b]	43	10	72	31
Grigordiu-Serbanescu et al. (1989)	47	Inpatient	61	Normals	72	72	10–17	K-SADS	10	1	61	25

[a] Mental Health Assessment Form (Kestenbaum and Bird 1978)
[b] Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978)

Table 3. Controlled studies of offspring of parents with unipolar depression[a]

Authors (Year)	Proband		Controls		Offspring				Lifetime disorders in offspring (rates/100)					
									Affective		Anxiety		Any DX	
	N	Source	*N*	Source	*N* Cases	*N* Controls	Age (years)	DX Interview	Cases	Controls	Cases	Controls	Cases	Controls
Welner et al. (1977)	29	Inpatient	41	School	75	152	6–16	DICA	7	0	–	–	–	–
Cytryn et al. (1982)	13	Inpatient	15	Normals	19	21	5–15	None	70	23	–	–	–	–
Keller et al. (1986)	57	Inpatient		Neighborhood	108	64	11–19	DICA	38	23	16	–	65	–
Beardslee et al. (1983)		Outpatient		Acquaintances										
Weissman (1987)	56	Inpatient Outpatient	35	Community	125	95	6–23	K-SADS	28	13	40	18	76	57
Hammen et al. (1987)	13	Female Outpatient	14 22	a) Medically ill b) Community	19	a) 18 b) 35	8–16	K-SADS	74	a) 44 b) 17	32	a) 17 b) 11	74	a) 50 b) 29
Turner et al. (1987)	11	Outpatient dysthymic	10	Advertisement	14	13	7–12	CAS[a]	0	0	21	9	22	8
Orvaschel et al. (1988)	34	Recurrent outpatient	29	Community	61	16	6–17	K-SADS	21	4	20	9	41	15
Sylvester et al. (1988)	45	Outpatient	26	Normals	11	47	7–17	DICA	29	5	34	6	–	–
Klein et al. (1986)	47	Inpatient	38 33	a) Psych ill b) Medically ill	47	38	14–22	SADS-L	32	0	–	–	51	24

[a] Child Assessment Schedule (Hodges et al. 1982)

the absence of cases of bipolar disorder or mania in these children is most likely attributable to the youthful age of these offspring, which averaged 14 years in these studies. Longitudinal data are necessary to determine the proportion of offspring in whom the expression of affective disorders and symptoms represents early manifestation of the same disorder for which their parents had sought treatment.

Table 3 summarizes the studies of offspring of parents with unipolar (or non-bipolar) affective disorder. There was an approximately fourfold increased risk of affective disorders, and a twofold increase in the rates of psychiatric syndromes in general among the offspring of depressed parents when compared to those of controls. In contrast to the offspring of bipolar parents, the children of unipolar parents exhibited an increased risk of diverse psychiatric disorders, including substance abuse, conduct disorder, and anxiety disorders. Indeed, in many studies, the rates and/or relative risks of the anxiety disorders exceeded those of the affective disorders. Thus, despite the elevated relative risk of affective disorders among offspring, the high rates of non-affective disorders suggest that there is less specificity of transmission of affective disorders among the unipolar than bipolar probands.

Although these studies provide evidence for the involvement of familial factors in the etiology of affective disorders, the observation of an increased risk of disorders in children sheds little light on possible mechanisms through which such factors may operate to produce depression and psychopathology in children. However, because a family history of depression has been the strongest and most potent non-demographic risk factor for the affective disorders, it is critical to include familial factors in systematic investigation of the etiology of affective disorders.

Risk factors for depression

Despite the abundant evidence for the role of positive family history in increasing the risk for major depression, studies which could implicate genetic mechanisms for familial aggregation have failed to provide evidence for a strong degree of heritability of non-bipolar depression. The bulk of evidence regarding the role of genetic factors in the etiology of the affective disorders has been derived from studies of manic or bipolar depression. The adoption studies of Cadoret et al. (1985), and twin studies of Kendler et al. (1986), Torgerson (1990), McGuffin et al. (1991), and Clifford et al. (1984) have revealed only weak evidence of transmission after adoption among children at biologic risk. Rather, these studies have shown that depression is associated with alcoholism or depression in the adoptive home, and thus have been more significant in demonstrating the importance of environmental contributants to depression (Goodwin et al. 1977). Furthermore, there are no trait markers or linkage studies which have suggested that there are major genetic factors involved in the etiology of non-bipolar affective illness. Although there is still a significant degree of heritability of affective syndromes, the degree of variance which can be attributed to genetic factors is quite low. An important caveat to this discussion is that the rate-limiting step in the genetic studies to date is the lack of valid definitions of non-bipolar depression, which may be comprised of a heterogeneous set of conditions, some of which are primary and others of which are secondary manifestations of personality disorders, abnormalities in neuroendocrine functioning, other disorders such as alcoholism or anxiety disorders, neurologic conditions including migraine, or developmental disorders.

Transmissible familial risk factors for depression

Parental psychopathology comprises the most powerful predictor of the subsequent development of depression in their offspring. The specific mechanism through which parental illness exerts an influence is not clear. Although some parental disorders exhibit specificity of transmission to offspring, as shown below, depression in parents is more strongly associated with anxiety disorders than with depression in children. The early expression of anxiety could constitute expression of an underlying vulnerability to emotional disorders through transmissible biologic factors, or the deficits in the home environment of children exposed to parental depression and its sequelae.

Several of the family studies of adolescents and children of depressed parents have incorporated measures of potential mechanisms for the familial transmission of affective disorders. In general, the findings converge in demonstrating that unipolar subtype, chronicity and severity of depression, and affective illness in the mother were associated with increased risk of disorders among the offspring. Most surprising, was the lack of specificity of transmission of non-bipolar depression, as revealed by elevation of non-affective disorders in the children. However, most of these family studies did not provide systematic information on comorbid disorders in the parents, thereby limiting conclusions regarding the specificity of transmission of affective and non-affective conditions.

Several family studies found that chronicity and severity of parental disorder was associated with an elevated risk of offspring. The mechanism for this observation is not clear. Increased severity could indicate greater underlying genetic risk or could be associated with greater disruption in the child's environment, or both. The features of the home environments which may potentiate or protect against the expression of depression in offspring have been reviewed by Rutter (1989), Angold (1988), and Downey and Coyne (1990). The family environment of depressed adults, particularly mothers, has been shown to be characterized by family and parental discord, divorce, inattention, rejection and abuse. Holmes and Robins (1988) reported that depressed women were more likely than alcoholic mothers to severely punish their children and to apply inconsistent pattern of interaction with their children. Similarly, prospective longitudinal studies of Cohen et al. (1990) showed that the combination of power-assertive punishment and lack of consis-

tency in parenting was more strongly related to the persistence of depression than was a family structure, in which the child was reared by only one parent, and by Parker (1979) who reported that the parental discipline pattern of affectionless control was strongly associated with depressive disorders in adolescents. Familial risk factors for depression in childhood were also investigated in the Zurich Cohort Study (Angst et al. 1990). The major predictors of depression were psychiatric illness in first-degree relatives, and lack of care and interpersonal conflict in parents.

An extensive review of the association between parenting behavior of depressed parents and child maladjustment revealed that the unidirectional model of intergenerational transmission of depression in insufficient to explain the lack of specificity of the parenting difficulties among depressed mothers. Indeed, chronic distress was found to have a more powerful influence on parenting behavior than clinical depression. Moreover, the impact of children's behavior on the maintenance of depression in parents has rarely been considered. There appears to be a reciprocal relationship between parental depression and child maladjustment (Downey and Coyne 1990).

There are several alternative models which link the effects of marital turmoil on parental depression and depression among exposed children. Downey and Coyne (1990) provide a detailed explication of possible alternatives, but evidence supporting the directionality and specific role of these factors in childhood depression is lacking. The effects of these phenomena on adolescents has received scant attention. Those studies that have investigated the effects of familial and individual characteristics on adolescents have tended to focus on the risk of externalizing conditions, particularly drug abuse. Information is clearly needed to gain understanding of the complex relationship between familial factors with individual factors in the etiology of the affective disorders.

Although parental concordance for psychiatric disorders has been studied fairly extensively among adult offspring of parents with psychopathology, the above-cited studies were quite variable in the degree to which the effects of the sex of the affected parent and the illness in the co-parent were assessed routinely. The studies that did examine the effect of sex of the parent yielded inconsistent findings; the study of Keller et al. (1986) revealed greater disturbance in the children of depressed mothers as compared to those of depressed fathers, whereas other studies reported no systematic differences in child psychopathology as a function of the sex of the affected parent (Weissman, 1987; Orvaschel et al. 1988). However, most of these studies did not simultaneously assess such factors as comorbidity and clinical severity, which may differ according to the sex of the affected parent.

The effect of dually affected parents in increasing the risk of psychopathology and difficulties in adjustment among their offspring appears to vary according to the specific disorders manifested by parents. A recent study of parental concordance for drug abuse revealed a strong monotonic trend in the risk of drug abuse among children (Merikangas et al. 1991). In contrast, most studies reveal a lack of specificity of the effect of parental concordance for psychopathology. That is, the risk of disorders among offspring of couples who exhibit concordance for specific disorders has not been shown to differ from that of couples who manifest different disorders, such as alcoholism in one parent and depression in the other (Merikangas et al. 1988). This suggests that the mechanism for the increased risk of illness among children may be associated with detrimental environmental factors produced by impairment secondary to the specific disorders manifest in the parents.

Environmental risk factors for depression

Environmental risk factors may be distinguished from non-transmissible familial factors according to the degree of sharing of environmental factors within families. Although marital and family discord may be shared among all family members, the negative effects could interact with individual susceptibility to stress to produce dramatically different outcomes in same-sex siblings who are close in age. Thus, the unique characteristics of each family member are critical in determining the effect of environmental phenomena on either elevating or diminishing the risk of manifestation of underlying liability factors for depression. It is these interactions that need to be the focus of future research on the etiology of affective syndromes, for it is clear that simplistic models of univariate external factors on the risk for depression are insufficient in explaining the etiology of such a common and relatively non-specific conditions.

Life events constitute the major source of unique environmental contributions to depression. The major events associated with depression in one longitudinal study were early separation from a parent by death or divorce, serious illnesses, particularly those which are chronic, and sexual and physical abuse (Reinherz et al. 1989). Other prospective longitudinal studies have failed to identify any specific life events or unique individual factors, aside from demographic factors, which appear to be causally related to depression.

Comorbidity of affective disorders: adults

In psychiatric disorders, comorbidity appears to be the rule rather than the exception. Numerous clinical studies have demonstrated the large proportion of patients who simultaneously meet diagnostic criteria for more than a single disorder, both within Axis I and between Axes I and II of the DSM-III-R. Similarly, epidemiologic surveys of the general population have shown that multiple diagnoses with individual subjects appear to be significantly more frequent than would be expected according to population base rates (Boyd et al. 1984). For example, mania is strongly associated with alcoholism among both men and women, with respective odds ratios (i.e., the ratio of the probability of an association to that of no association) of 6.3 and 10.0.

Comorbidity may affect linkage studies by leading to misclassification of probands or relatives. That is, when

a comorbid disorder modifies the expression of an affective disorder, it leads to misclassification of an affected individual as unaffected or false-negative errors in phenotype assignment. Such errors may lead to erroneous estimates of the lod scores, the quantitative indicator of linkage.

Comorbidity of depression and other disorders: children

Evidence from clinical, epidemiologic, longitudinal and family study data consistently demonstrates that affective disorders in adolescents are characterized by a substantial degree of comorbidity, particularly with anxiety disorders and conduct problems. The majority of adolescents with depressive disorders exhibit concomitant disorders in either the emotional or behavioral spheres. Anxiety disorders are the most common concomitant to depression in both childhood and adolescence, with as many as 75% of depressed adolescents reporting anxiety disorders as well. Studies of clinical samples of adolescents with depression and those with anxiety disorders including phobia, separation anxiety, and overanxious disorder reveal a high degree of co-occurrence between symptoms and disorders in each of the two domains (Bernstein 1991; Strauss et al. 1988; Mitchell et al. 1988; Kovacs et al. 1989; Bernstein and Garfinkel 1986). Epidemiologic studies of adolescents reveal that the anxiety disorders are the conditions by far most commonly associated with depression affecting approximately 20–75% of subjects with depression. Similarly, conduct disorders are also frequently associated with depression in community samples, with an average of 33% of adolescents with depression also having a history of conduct disorders.

An association between affective disorders and other psychiatric and non-psychiatric disorders has also been reported among adolescents identified in epidemiologic samples. For example, the prevalence of affective disorders has been shown to be significantly greater among adolescents with eating disorders, substance abuse (Rohde et al. 1991), and attention deficit disorder (McClellan et al. 1990). An association between depression and somatic illnesses, particularly those involving the central nervous system (Rutter et al. 1976), such as migraine (Merikangas et al. 1990), has also been reported.

Comorbidity in family studies

Although comparable twin data have not been reported among adolescents, some of the family studies of adolescent offspring of parents with depression or anxiety disorders provide evidence regarding the co-transmission of these conditions. A review of the association between affective and anxiety disorders in family studies of parents with affective or anxiety disorders was presented by Weissman (1990). She concluded that anxiety and depression co-occur both within children and adolescents and in their families. However, this review did not present a mutually exclusive categorization of anxiety and depression among the offspring.

In order to investigate the degree of co-transmission between the disorders, it is necessary to classify the diagnoses in the offspring in mutually exclusive categories. The results of controlled family studies of adolescents in which these data were available are presented in Table 4. These studies reveal a lack of specificity of transmission of depression because of the low rates of pure depression among the offspring. The prevalence of pure anxiety disorders was greater than that of pure depressive disorders among the offspring of depressed parents. When depression was manifest among the offspring of parents with anxiety disorders, it often co-occurred with depression.

Similarly, the studies which have investigated the prevalence of anxiety and depression among parents of depressed adolescents reveal a lack of specificity of expression of depression. Mitchell et al. (1989) reported that a maternal history of anxiety or substance abuse was associated with depression in the offspring. Major depression in neither father nor mother was associated with an increased risk of depression among the offspring relative to the controls.

This was confirmed in an extensive analysis of the transmission of depression and anxiety in a family study,

Table 4. Comorbidity in offspring in controlled family studies of parents with depression or anxiety

Authors (Year)	Proband groups		DX in offspring (rates/100)		
	N Parents	*N* Children	Depression and anxiety	Depression only	Anxiety only
Decina et al. (1983)	18 Bipolar	31	12.9%	12.9%	3.2%
	14 Controls	16	–	–	–
Turner et al. (1987)	13 Anxiety	16	0	6.3%	37.5%
	11 Dysthymic	14	0	0	21.4%
	10 Normal	13	0	0	9%
Merikangas et al. (1988)	33 Both Dep and Anx or 1 Dep/1 Anx	77	63.6%	18.1%	32.5%
	30 One Dep and Anx	71	16.9%	16.9%	19.7%
	5 One Dep	9	22.2%	11.1%	22.2%
	4 One Anx	10	10.0%	0	10.0%
	20 Both Normal	52	7.7%	17.3%	9.6%
McClellan et al. (1990)	16 Depression	27	34%	18%	27%
	29 Panic	50	27%	12%	23%
	26 Normal	48	20%	11%	13%

Table 5. Effects of logistic regression analysis of parental diagnosis on disorders in offspring

Main effects		Disorders in offspring [adjusted odds ratio (±95% confidence intervals)]			
		Major depression	Depression only	Anxiety only	Anxiety and depression
Diagnosis in mother	Depression	N.S.	N.S.	N.S.	N.S.
	Anxiety	N.S.	N.S.	N.S.	4.2 (1.7–10.6)
	Alcoholism	4.8 (1.5–15.8)**	N.S.	N.S.	N.S.
Diagnosis in father	Depression	N.S.	N.S.	6.7 (2.3–19.8)**	N.S.
	Anxiety	N.S.	N.S.	0.4 (0.1– 1.0)	N.S.
	Alcoholism	N.S.	N.S.	N.S.	N.S.
Parent proband		N.S.	N.S.	0.1 (0.03–0.4)**	N.S.
Age of offspring (continuous)		***	***	**	**
Sex of offspring		2.2 (1.2–4.2)*	N.S.	N.S.	3.5 (1.3–7.0)*
Interactions	Depression mother × anxiety mother	N.S.	N.S.	7.9 (2.6–23.8)**	N.S.
	Anxiety mother × anxiety father	3.1 (1.5–6.5)**	N.S.	N.S.	N.S.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; N.S., not significant

in which the joint effects of parental comorbidity and mating type for these conditions on comorbidity among the adolescent offspring were examined (Table 5) (Merikangas et al. 1988). Although the original design of the study focused on the risk of depression among offspring of parents in treatment for major depression, stronger transmissibility was found for anxiety disorders plus depression than for major depression alone. Indeed, there was no association between parental depression and depression alone among offspring. The only parental diagnosis associated with an increased risk of depression in offspring was maternal alcoholism.

These findings confirm the overlap in the transmission of depression and anxiety shown in the other studies summarized in Table 5, as well as those in family studies of adult relatives of probands with affective disorders. Moreover, retrospective data on the adolescent offspring in this study suggest that anxiety may constitute an early form of expression of affective disorders. The lack of transmission of "pure depression" suggests that depression among the adolescent offspring may result from non-transmissible factors, either familial or unique to the individual child. The results of an earlier uncontrolled study of offspring of bipolar parents by Conners et al. (1979) also revealed that anxiety symptoms tended to precede those of depression, particularly among the female offspring of unipolar probands. The lack of such an association among the offspring of bipolar probands was interpreted as differential manifestation of genetic susceptibility underlying the expression of bipolar disorder and unipolar disorder. Whereas children of bipolar probands tend to manifest few symptoms and mainly within the affective domain, children of unipolar probands exhibit more diverse symptom patterns.

Potential contributions of genetic studies of the affective disorders

The failure to identify the genetic mechanisms of the affective disorders to date does not imply that the discovery of such genes is a phenomenon in the distant future. Recent developments in the understanding of human cancers, including an early-onset form of breast cancer, and retinoblastoma, demonstrate the importance of inheritance of genetic factors which, in the presence of particular environmental factors, lead to the development of disease. The background research which led to these findings illustrates the strength of the combined approach of genetic epidemiology and molecular genetics to gain understanding of the gene-environment interactions involved in the pathogenesis of complex diseases (Hall et al. 1990; Friend et al. 1986).

Table 6. Application of linkage markers to case-control studies of children and adolescents

Genetic markers	Risk factor A	Disorder	Interpretation
Present	Present	Present	G×E
		Absent	Non-penetrant; Protective factor
	Absent	Present	G
		Absent	Non-penetrant
Absent	Present	Present	E
		Absent	Not risk factor A
	Absent	Present	Other risk factor
		Absent	Control

Perhaps the next step towards elucidating the role of genetic factors in depression is to focus on the components of depressive disorder, particularly those which can be assessed quantitatively. The use of family study paradigms to examine the specificity of transmission of the components or putative markers of depression is a necessary step before attempting to employ linkage analyses of these conditions. Moreover, these data may also be required for the development of definitions of depression and its subtypes, for which the lack of validity appears to be the rate-limiting step in applying the powerful tools of molecular biology and statistical genetics to this fascinating yet perplexing condition.

Once genetic markers for the major affective disorders have been identified, the high-risk study design will provide an unprecedented opportunity to elucidate the environmental conditions that potentiate or suppress the expression of underlying vulnerability. Possible study designs for this purpose are shown in Table 6. Similar to the application of cross-fostering studies to identify the role of genetic (G) and environmental (E) factors and their interaction (G × E) in the etiology of a disease, information on children with biologic vulnerability will enable discrimination between extrinsic genetic, biologic and environmental contributions to the etiology of depression. Moreover, the development of affective symptomatology in children who do not possess the genetic markers can be used to identify environmental mechanisms in the etiology of depression. Susceptible children could also be examined prospectively to elucidate the early signs and patterns of expression of affective disorders. Perhaps the most important implication of the identification of genetic markers for affective disorders is the opportunity for prevention of the disorders. Early identification of youngsters who do manifest early signs of the disorders, would facilitate secondary and tertiary prevention of the consequences of these distressing conditions.

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