

Models for the Joint Effect of Genotype and Environment on Liability to Psychiatric Illness

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The authors present three major models for the joint effect of genes and environment on liability to psychiatric illness: additive effects of genotype and environment, genetic control of sensitivity to the environment, and genetic control of exposure to the environment. Each model is illustrated by several examples, including a quantitative one. The authors attempt to demonstrate that genes and the environment can interact in several interesting and potentially subtle ways, that these interactions can be expressed in simple models from which clear empirical predictions can be generated, and that elucidation of the etiology of psychiatric disorders will require the consideration of both genetic and environmental risk factors.

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Studies investigating the role of genetic and environmental factors in the etiology of psychiatric illness have, with notable exceptions (1–3), been conducted in isolation. However, empirical support for an etiologic role of genetic factors in most psychiatric disorders continues to increase (4–7). At the same time, researchers (8–11) have identified an increasing number of environmental factors that play a causative role in psychiatric illnesses. In making a comprehensive etiologic model for psychiatric illness we must recog-

nize the joint effect of genetic *and* environmental risk factors.

In this paper we examine how genetic and environmental risk factors might interact in the causation of psychiatric illness. Three basic models are described, each of which represents a fundamentally different way in which genes and environment may jointly influence the liability to psychiatric illness. Although our goal is heuristic, quantitative examples illustrate features of these models that are difficult to convey in other ways. Technical aspects of the models are presented in appendix 1.

GENERAL CHARACTERISTICS OF THE MODELS

The genetic and environmental parameters of these models are designed to be simple and not necessarily realistic. The genetic mode of transmission is assumed to be a single locus with two possible alleles, *A* and *a*. Since we assume that this locus is not on a sex chromosome, everyone in the population will have two “copies” of the locus and one of three possible genotypes: *AA*, *Aa*, and *aa*. We further assume that the population mates randomly, the fitness of the genotypes is equal, and the probability of illness is unrelated to age or sex.

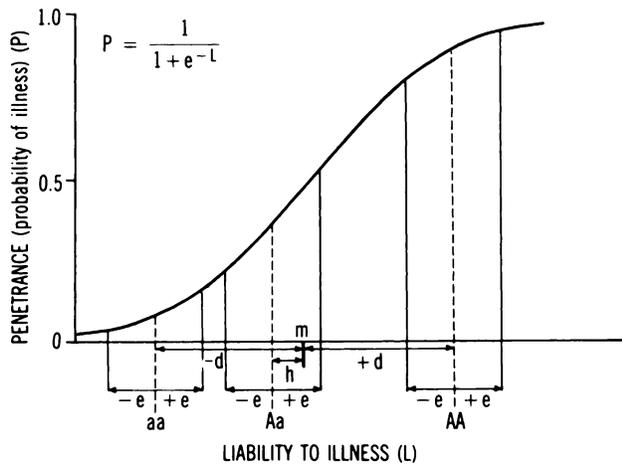
The environment occurs in these models in one of two mutually exclusive states, which are called the protective environment and the predisposing environment. Exposure to the protective environment diminishes while exposure to the predisposing environment increases the probability of illness. Environmental exposure is assumed to be random and is therefore uncorrelated among relatives (except when there is a genetic influence on environmental exposure). We make no assumptions about the possible temporal relationship between environmental exposure and onset of illness.

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FIGURE 1. Relationship Between Liability to Illness and Penetrance Given Additive Effects of Genotype and Environment^a



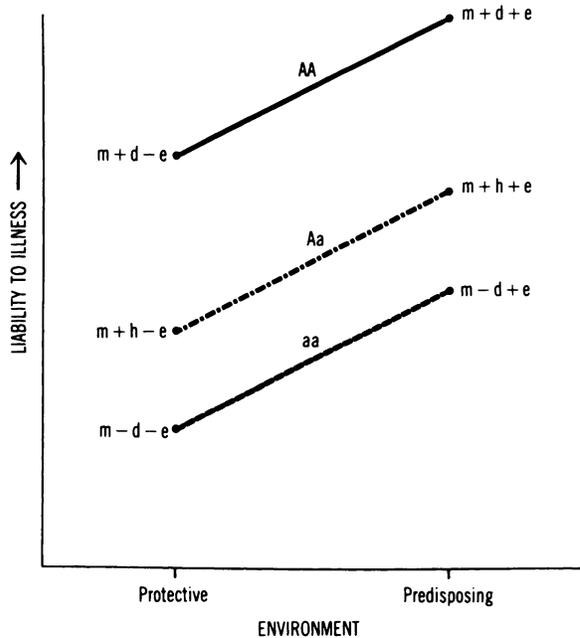
^a*m* is the midhomozygous point, *d* and *h* are the additive and dominance genetic effects, respectively, which in this model directly affect liability to illness, and *e* is the environmental effect; see appendix 1 for details.

Each model assumes that an individual's genotype and environmental exposure contribute to a latent variable termed "liability" to illness. Individuals with a high liability have a high probability of illness, while the opposite is true for individuals with low liability. The precise mathematical relationship between liability and probability of illness can take numerous forms. In these models the logistic function is used (see appendix 1). For each specific model the genetic and environmental contribution to liability is expressed with the notation of biometrical genetics (13) (for details see appendix 1). Figure 1 displays this function for the first, or additive, model. It is important to remember that the characteristics of the models are expressed in terms of liability to, not probability of, illness.

BASIC MODELS

The three basic models are 1) additive effects of genotype and environment, 2) genetic control of sensitivity to the environment, and 3) genetic control of exposure to the environment. For each of these three models the main features of the model are presented, followed by two hypothetical, nonnumerical examples of the model (one from general genetics and one from psychiatry) and one, more detailed numerical example. To illustrate the implications of the specific models the numerical examples include the risk of illness in monozygotic (identical) co-twins and siblings of affected individuals as a function of the environmental exposure of the proband and relative. Monozygotic twins are used in these illustrations because of the great power they provide for discriminating models and the long tradition of their use in psychiatric

FIGURE 2. Liability to Illness as a Function of Genotype and Environment With Additive Effects of Genotype and Environment^a



^a*m* is the midhomozygous point, *d* and *h* are the additive and dominance genetic effects, respectively, which in this model directly affect liability to illness, and *e* is the environmental effect; see appendix 1 for details.

genetics (4). The numerical examples were chosen to illustrate important features of the models. While not specifically designed to accurately depict any particular real disorder, the results obtained were typical of those found with the models given most plausible parameter values.

Additive Genetic and Environmental Effects

This model, which is depicted in figure 2, represents the "common sense" way of thinking about genes and environment and hypothesizes that liability to illness results from the simple addition of the genetic and environmental contributions. This model has two central characteristics. First, the effect of exposure to a given environment on liability to illness is the same regardless of genotype. This feature of the model is expressed in figure 2 by the fact that the slopes of the lines are the same for all three genotypes. The second central feature of this model is that the probability of an individual's exposure to a given environment is independent of the individual's genotype.

Example 1. Assume there is a gene locus that influences the risk for stomach cancer. Individuals with genotypes AA, Aa, and aa are at, respectively, high, intermediate, and low risk of developing this tumor. High intake of smoked meats represents a predisposing environment for this condition, while the absence of such items in a diet constitutes a protective environment. The increase in liability associated with a high

TABLE 1. Model of Additive Effects of Genotype and Environment^a

Variable	Random Environment	Protective Environment	Predisposing Environment
Penetrance for each genotype (%)			
AA	76.0	74.8	96.7
Aa	1.7	1.2	10.7
aa	0.6	0.4	3.8
Proportion of affected with each genotype (%)			
AA	49.8	58.1	16.2
Aa	19.8	16.8	32.2
aa	30.4	25.2	51.6
Risk in relatives (%) as a function of environmental exposure of proband ^b			
Monozygotic co-twin	38.3	44.5	13.1
Sibling	12.8	14.6	5.4
Risk in relatives (%) as a function of environmental exposure of both proband and relative			
Environmental exposure of monozygotic co-twin			
Protective environment		43.7	12.7
Predisposing environment		58.9	21.0
Environmental exposure of sibling			
Protective environment		14.2	5.0
Predisposing environment		23.4	11.4

^aFrequency of A allele=10%; frequency of predisposing environment=5%.

^bThe ratio of the risk to a monozygotic co-twin and sibling when the proband was exposed to a protective versus a predisposing environment is, respectively, 3.4 and 2.7.

intake of smoked meats is the same for all three genotypes. An individual's genotype is unrelated to the probability of his consuming large amounts of smoked meats.

Example 2. A gene for schizophrenia is found, and individuals with genotypes AA, Aa, and aa are at high, intermediate, and low risk for the disorder. Head trauma constitutes a predisposing environment for schizophrenia, while its absence is protective. The increase in liability to schizophrenia associated with head trauma is the same regardless of the individual's genotype, and the individual's genotype has no influence over the probability that he will suffer head trauma.

Numerical example. We take as our parameters in the protective environment those of the single major locus model for schizophrenia proposed by Kidd and Cavalli-Sforza (15). The frequency of the predisposing environment is set at 5%, and the magnitude of the environmental effect is adjusted so that the heritability of liability for schizophrenia equals 70%, in accord with recent estimates (16). The remaining 30% of variance in liability results from the identified environmental factor. The penetrance for each genotype (which is the probability that an individual with that genotype will be affected), the proportion of affected individuals with each genotype, and the risk of illness in relatives as a function of the environmental exposure can then be calculated. Three different environmental exposures are considered: random (i.e., 95% protective environment, 5% predisposing environment), only the protective environment, and only the predisposing environment.

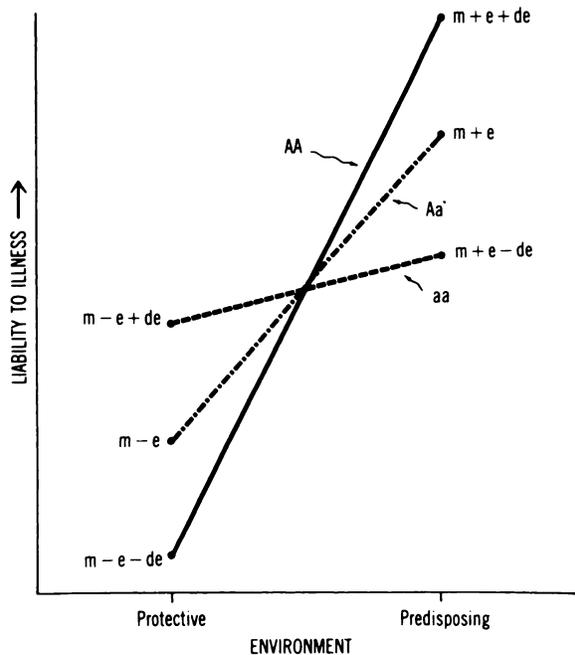
As expected, the penetrance for each of the three genotypes is greater in the predisposing environment than in the protective environment (table 1). The distribution of genotypes in affected individuals differs

in the two environments. In the protective environment 58% of the affected individuals have the "high-risk" genotype (AA), while only 25% have the "low-risk" genotype (aa). In the predisposing environment only 16% of the affected individuals have the high-risk genotype, while over 51% have the low-risk genotype. Individuals who become affected in a predisposing environment have on average a lower genetic risk for illness than individuals who become ill in a protective environment.

The risk of illness in relatives of probands chosen at random with regard to environmental exposure is much higher than the risk of illness in the population (1.55%). When the heritability of liability is high, the additive model is consistent with a high degree of familial aggregation for a disorder. However, the risk of illness is much lower in relatives of individuals who became affected in a predisposing environment than in relatives of individuals who became affected in a protective environment (table 1). For example, monozygotic co-twins of probands exposed to a predisposing environment have a risk of illness of 13.1%, whereas the monozygotic co-twins of probands exposed to a protective environment have a risk of 44.5%. This pattern results from the fact that affected individuals from a protective environment have on average a higher genetic risk for illness than do affected individuals from a predisposing environment. This higher genetic risk is passed on to their relatives, resulting in a greater risk for illness among relatives of affected individuals from a protective versus predisposing environment.

When both the proband and the relative are classified by environmental exposure, the highest risk of illness is found in relatives of probands exposed to a protective environment who themselves have been exposed to a predisposing environment. The lowest

FIGURE 3. Liability to Illness as a Function of Genotype and Environment With Genetic Control of Sensitivity to the Environment^a



^a*m* is the midhomozygous point, *d* is the additive genetic effect, which in this model affects the sensitivity of the individual to the environment, and *e* is the environmental effect; see appendix 1 for details.

risk of illness occurs in relatives of probands who became ill in a predisposing environment who themselves are exposed to a protective environment. This relationship is the same in monozygotic co-twins and siblings except that for every category the risk of illness is higher in the monozygotic co-twins.

Genetic Control of Sensitivity to the Environment

In this model genes do not directly alter the probability of illness. Rather, they control the degree to which the individual is sensitive to the risk-increasing or risk-reducing aspects of the environment. Genetic control of sensitivity to the environment, which is depicted in figure 3, provides an explanation for most examples of what have been termed genotype-environment interactions (13). Allele *A* conveys sensitivity and allele *a* insensitivity to the environment. Sensitivity to the environment is depicted as the slope of the line in figure 3, which differs markedly among genotypes. Individuals with an *AA*, or "sensitive," genotype have the steepest slope, indicating the greatest increase in liability in the predisposing environment and the greatest decrease in the protective environment. Individuals with the *aa*, or "insensitive," genotype have the flattest slope, and their liability to illness increases only slightly in the predisposing environment and decreases only slightly in the protective environment. As in the additive model, in this model genes do not influence

the probability of exposure to a predisposing environment.

While most easily conceptualized as genetic control of sensitivity to the environment, this model can also be expressed as environmental control of gene expression. In this model the nature of gene action differs among environments. In the predisposing environment allele *A* increases risk for illness, while in the protective environment the same allele decreases risk for illness. The environment is altering the ways in which genes influence risk of illness.

Example 1. The effect of sodium intake on blood pressure is quite variable among individuals, and this variability may in part be under genetic control (17). Assume a gene has been identified that is responsible for this variability. The blood pressure of individuals with an *AA* genotype is very sensitive to alterations in sodium intake, increasing to hypertensive levels with high-sodium diets (i.e., a predisposing environment) and decreasing to low levels with low-sodium diets (i.e., a protective environment). By contrast, the blood pressure of individuals with an *aa* genotype changes very little as a function of sodium intake. Averaged across all diets, however, the blood pressures of individuals with the *AA* and *aa* genotypes do not differ substantially. The genotype has no influence on sodium intake.

Example 2. The effect of life events on the risk for depression differs considerably among individuals (8, 11). Assume a gene has been identified that is responsible for this variation. Stressful events (a predisposing environment) increase markedly the risk for depression in individuals with an *AA* genotype. However, in a low-stress, or protective, environment individuals with this genotype are at very low risk for depression. By contrast, in individuals with an *aa* genotype the risk for depression is only mildly increased by a stressful environment and only mildly decreased in a low-stress environment. However, the risk for depression averaged across all environments is not markedly different in individuals with *AA* and *aa* genotypes. An individual's genotype is unrelated to his probability of experiencing a stressful environment.

Numerical example (table 2). We set the frequency of the *A* allele at 10% and the frequency of the predisposing environment at 50%. Penetrance is adjusted until the proportion of variance in liability accounted for by the environment (30%) is the same as in the additive model. However, in this model the genotype-environment interaction now accounts for the remaining 70% of the variance in liability. In the predisposing environment penetrance increases as the genotype goes from *aa* to *Aa* to *AA*. However, in the protective environment penetrance decreases over the same genotypes. Thus, the *AA* genotype has the highest penetrance in the predisposing environment but the lowest in the protective environment. The penetrance of the *aa* genotype is almost the same in the two environments.

The distribution of genotypes in affected individuals

TABLE 2. Model of Genetic Control of Sensitivity to the Environment^a

Variable	Random Environment	Protective Environment	Predisposing Environment
Penetrance for each genotype (%)			
AA	44.6	0.1	89.2
Aa	17.6	1.5	35.0
aa	2.8	2.3	3.4
Proportion of affected with each genotype (%)			
AA	7.6	0.1	8.9
Aa	53.7	1.4	63.4
aa	38.7	98.5	27.5
Risk in relatives (%) as a function of environmental exposure of proband ^b			
Monozygotic co-twin	13.9	3.0	15.9
Sibling	9.8	4.4	10.9
Risk in relatives (%) as a function of environmental exposure of both proband and relative			
Environmental exposure of monozygotic co-twin			
Protective environment		2.2	0.7
Predisposing environment		3.8	31.2
Environmental exposure of sibling			
Protective environment		2.0	1.3
Predisposing environment		6.8	20.4

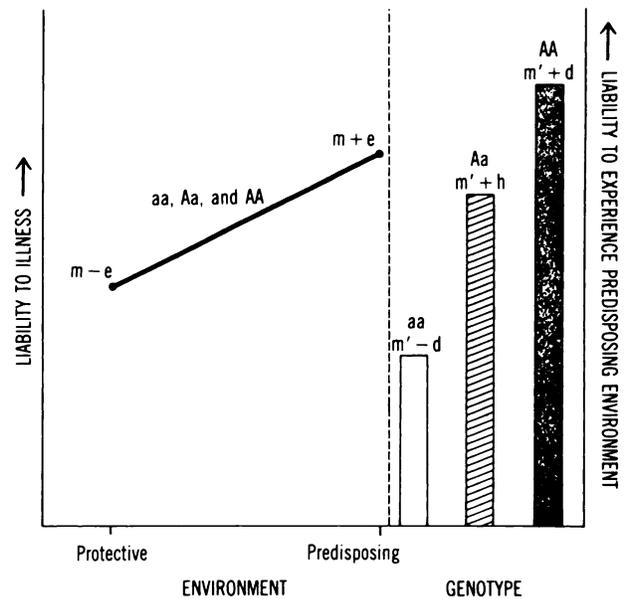
^aFrequency of A allele=10%; frequency of predisposing environment=50%.

^bThe ratio of the risk to a monozygotic co-twin and sibling when the proband was exposed to a protective versus a predisposing environment is, respectively, 0.2 and 0.4.

from the two environments is now strikingly different. In the predisposing environment 27.5% of the affected individuals have the *aa*, or insensitive, genotype, while in the protective environment the parallel figure is over 98%. Most individuals who become ill in a predisposing environment have a relatively sensitive genotype (i.e., *AA* or *Aa*), while nearly all individuals who become ill in a protective environment have the insensitive (i.e., *aa*) genotype.

The risk of illness in relatives of affected individuals randomly distributed over environments (9.8%–13.9%) is modestly greater than the risk in the general population (5.9%). In general, the degree of familial aggregation in this model is less than that found in the additive model, especially when the predisposing environment is relatively rare. In contrast to the additive model, the risk of illness in relatives is now greater if the proband is exposed to a predisposing environment than if he is exposed to a protective environment. For example, the risk of illness in a monozygotic co-twin of a proband from a protective environment is only 3.0%, while if the proband is from a predisposing environment the risk is 15.9%.

When both the proband and relative are categorized on the basis of their environmental exposure, the highest risk of illness in both monozygotic co-twins and siblings is found when both the proband and relative have been exposed to a predisposing environment. When both the proband and relative have been exposed to the same environment (i.e., either protective or predisposing), the risk of illness is higher in monozygotic co-twins than siblings. However, when the environmental exposures of the proband and relative differ, the risk of illness is higher in the siblings than in the monozygotic co-twins. For example, if the proband is exposed to a protective environment and the relative to a predisposing environment, the risk of

FIGURE 4. Liability to Illness as a Function of Genotype and Environment With Genetic Control of Exposure to the Environment^a

^a m is the midhomozygous point for liability to illness, m' is the midhomozygous point for liability to experience the predisposing environment, d and h are the additive and dominance genetic effects, respectively, which in this model affect the liability to experience the predisposing environment, and e is the environmental effect; see appendix 1 for details. The left side of the figure demonstrates that the liability to illness is independent of genotype. The right side of the figure demonstrates that liability to experience the predisposing environment depends on genotype.

illness is 3.8% in monozygotic co-twins and 6.8% in siblings. This seemingly paradoxical finding can be explained as follows: 1) individuals who become ill in a protective environment usually have an insensitive

TABLE 3. Model of Genetic Control of Exposure to the Environment^a

Variable	Random Environment	Protective Environment	Predisposing Environment
Penetrance for each genotype (%)			
AA	25.3	0.5	50.0
Aa	3.0	0.5	50.0
aa	0.7	0.5	50.0
Proportion of affected with each genotype (%)			
AA	70.4	8.9	75.6
Aa	24.9	51.0	22.7
aa	4.7	40.0	1.7
Risk in relatives (%) as a function of environmental exposure of proband ^b			
Monozygotic co-twin	18.6	4.1	19.8
Sibling	11.1	5.0	11.7
Risk in relatives (%) as a function of environmental exposure of both proband and relative			
Environmental exposure of monozygotic co-twin			
Protective environment		0.5	0.5
Predisposing environment		50.0	50.0
Environmental exposure of sibling			
Protective environment		0.5	0.5
Predisposing environment		50.0	50.0

^aFrequency of A allele=40%; frequency of predisposing environment=10.6%.

^bThe ratio of the risk to a monozygotic co-twin and sibling when the proband was exposed to a protective versus a predisposing environment is, respectively, 0.2 and 0.4.

genotype, 2) because monozygotic twins share all their genes and siblings on average share only half of them, more monozygotic co-twins than siblings of probands with an insensitive genotype will themselves have an insensitive genotype, and 3) individuals with an insensitive genotype are at particularly low risk for illness, relative to other genotypes, in a predisposing environment.

Genetic Control of Exposure to the Environment

In the preceding models the probability of exposure to a given environment was independent of genotype. By contrast, in this model, the genotype's only influence on the liability to illness is to alter the probability of exposure to a predisposing environment (figure 4). In other words, while in the previous models the environmental exposure of an individual was uncorrelated with his genotype, in this model genes and environment are correlated.

As outlined in figure 4, the liability to experience a predisposing environment is greatest with the AA genotype and least with the aa genotype. However, once exposed to either a protective or predisposing environment, the liability to illness does not differ between genotypes.

Example 1. Genetic factors influence the probability of smoking (18). Assume that this is due to a single gene that causes the AA genotype to have the highest and the aa genotype the lowest liability to smoke. Since smoking is a predisposing environment for lung cancer, an AA genotype will be at higher and an aa genotype at lower risk for this disease. However, this gene does not directly influence the liability to lung cancer. If a person with an aa genotype happens to smoke, his risk for cancer will be no lower than that of any other smoking individual. Similarly, an AA indi-

vidual who does not smoke will have as low a risk for lung cancer as any nonsmoker.

Example 2. As already noted, adverse life events predispose an individual to depression (8, 11). Genetic influences on human personality have been repeatedly demonstrated (19). Clinical experience suggests that individuals differ considerably in the degree to which certain life events occur around them. These differences probably result from personality traits such as impulsiveness, personal stability, and frustration tolerance. Assume a gene has been identified that influences this mixture of personality traits. An individual with an AA genotype is impulsive and unstable and has many life events such as job and relationship changes. By contrast, an individual with an aa genotype is consistent and stable and has few such life events. An AA genotype may thus predispose an individual to depression, but only by increasing the chance of experiencing life events. Given the presence of a life event, there is no difference in risk of illness between a person with an AA genotype and one with an aa genotype.

Numerical example (table 3). We assume that individuals with the AA, Aa, and aa genotypes have 50%, 5%, and 0.5% probabilities of exposure to a predisposing environment. Once exposed to a predisposing environment, all individuals have a 50% chance of becoming affected. Individuals exposed to a protective environment have only a 0.5% chance of becoming affected. The frequency of the A allele is 40%.

In either the protective or predisposing environment the penetrance does not differ between genotypes. However, under the random environment condition the penetrance of the AA genotype (25.3%) is much greater than for the aa genotype (0.7%). If one were unaware of the effect of allele A on environmental exposure, it would look as if this allele directly increased the risk for illness. The genotypic distribution

of affected individuals again differs considerably between the predisposing and protective environments. In the protective environment 8.9% of the affected individuals have an AA or "predisposing-environment-seeking" genotype, while in the predisposing environment the parallel figure is 75.6%.

The risk of illness in relatives of randomly chosen affected individuals (11.1%–18.6%) is considerably higher than the risk in the general population (5.7%). When the predisposing environment carries a much greater risk of illness than the protective environment and the differences between genotypes in probability of exposure to the predisposing environment are large, this model can be consistent with a high degree of familial aggregation. As in the "sensitivity" but not the "additive" model, in this model the risk of illness is much higher in relatives of probands who become ill in a predisposing versus in a protective environment. This is because individuals who become ill in a predisposing environment have a much higher chance of having an AA genotype than those who became ill in a protective environment. Therefore, relatives of affected individuals from a predisposing environment are more likely to have a genotype that will cause them to become exposed to a predisposing environment, which will in turn increase their risk for illness.

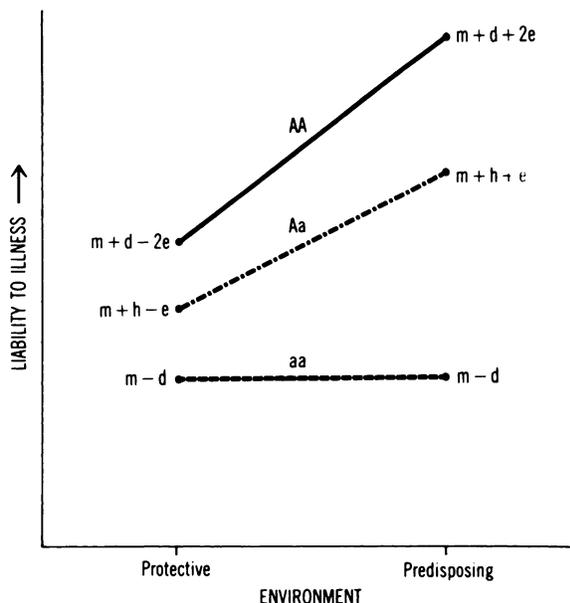
The most revealing feature of this model is demonstrated when both probands and relatives are divided on the basis of environmental exposure. When this occurs, the risk of illness is *entirely* determined by the environment to which the relative has been exposed. Neither the nature of the genetic relationship with the proband nor the environmental exposure of the proband has any impact on the relative's risk of illness. This is because in this model genes act only by altering the probability of environmental exposure. Once this exposure is controlled for, genes no longer play any role in determining the risk of illness.

A further unique feature of this model is that environmental exposure is correlated in relatives as a function of the degree of genetic relationship. While only 10.6% of the general population is exposed to a predisposing environment, the monozygotic co-twin of an individual with a predisposing environment has a 38.9% chance of exposure to a predisposing environment. For a sibling the parallel figure is 22.5%.

MORE COMPLEX MODELS

The joint effect of genes and environment in the etiology of psychiatric illness may not often be accounted for entirely by one of the three basic models. In this section our intent is to briefly present, without numerical examples, two particularly interesting more complex models: genetic control of mean liability to illness (as seen in the additive model) *and* sensitivity to the environment and genetic control of mean liability to illness *and* probability of exposure to the environment.

FIGURE 5. Liability to Illness as a Function of Genotype and Environment With Genetic Control of Mean Liability to Illness and Sensitivity to the Environment^a



^a m is the midhomozygous point, d and h are the additive and dominance genetic effects, respectively, which in this model directly affect liability to illness, and e is the environmental effect. In this model, sensitivity to the environment is also altered by the genotype, as reflected by the fact that the environmental effect is doubled in the AA genotype and absent in the aa genotype. See appendix 1 for details.

Genetic Control of Mean Liability to Illness and Sensitivity to the Environment

In this model, which is a combination of the first and second basic models, genes influence both the mean liability to illness and the sensitivity of the individual to the environment. As seen in figure 5, a particularly plausible form of this model is that the A allele conveys both a higher risk of illness and a higher sensitivity to the environment.

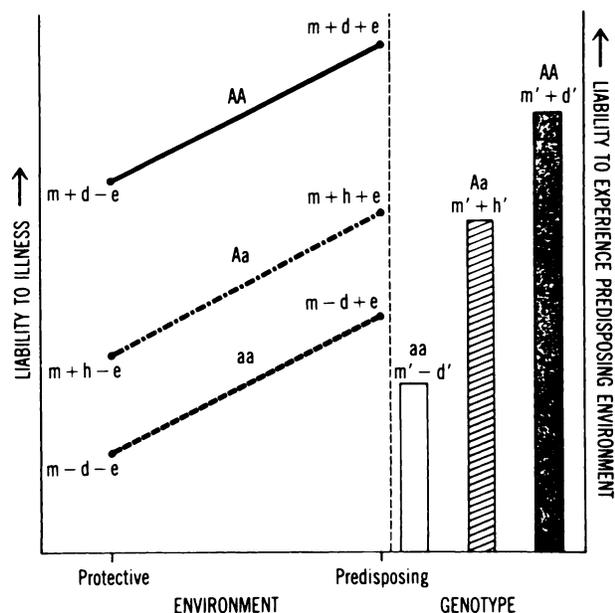
Example. The A allele might cause a higher liability to schizophrenia *and* a greater sensitivity to possible schizophrenogenic aspects of the environment, such as head trauma. Thus, AA individuals have a higher mean liability to schizophrenia than do aa individuals. In addition, AA individuals have a greater increase in liability associated with exposure to a predisposing environment than do aa individuals.

Genetic Control of Mean Liability to Illness and Probability of Environmental Exposure

In this model, which is a combination of the first and third basic models, genes influence both the mean liability to illness and the probability of exposure to the predisposing environment (figure 6).

Example. The A allele affects certain personality traits that increase the average risk for depression but

FIGURE 6. Liability to Illness as a Function of Genotype and Environment With Genetic Control of Mean Liability to Illness and Exposure to the Environment^a



^a*m* is the midhomozygous point for liability to illness, *m'* is the midhomozygous point for liability to experience the predisposing environment, *d* and *b* are the additive and dominance genetic effects, respectively, on liability to illness, *d'* and *b'* are the additive and dominance genetic effects, respectively, on liability to experience the predisposing environment, and *e* is the environmental effect; see appendix 1 for details. The left side of the figure demonstrates that the liability to illness is a result of the additive effects of genotype and environment. The right side of the figure demonstrates that liability to experience the predisposing environment depends on genotype.

also increase the probability of life events that themselves may precipitate a depression. Therefore, in this model genes have two “paths” to altering the probability of disease. They may alter it directly, by increasing risk for illness independent of environment, and they may alter the probability of exposure to a predisposing environment, which will in turn increase the likelihood of illness.

The properties of these complex models are a mixture of the characteristics of the two basic models from which they are made. Depending on the exact features of these complex models, they will resemble one or another of the basic models. However, since certain of the predictions of the simpler models are opposite to one another, there are circumstances in which their effects can in part cancel each other out.

DISCUSSION

The joint effect of genes and environment in the etiology of psychiatric illness may take three fundamental forms: 1) genes and environment may contribute additively to liability to illness, 2) genes may

control sensitivity to the environment, and 3) genes may alter the probability of exposure to environments. The second model may also be conceptualized as environmental control of gene expression. These three basic models all have qualitatively different predictions for the risk of illness in monozygotic co-twins and siblings when *both* the proband and the relative can be categorized by their environmental exposures. In the additive model the risk of illness is highest when the proband was exposed to a protective environment and the relative to a predisposing environment, and all risks are higher in monozygotic co-twins than in siblings. With the genetic control of sensitivity to the environment, risk is highest when both proband and relative have been exposed to a predisposing environment, and risk is higher in monozygotic co-twins than in siblings only when both proband and relative have been exposed to the same kind of environment. With genetic control of environmental exposure, the risk of illness in relatives is only a function of the environmental exposure of the relative.

The models presented are simplistic. Genetic effects are restricted to a single locus, while it is probable that at least several loci influence liability to most psychiatric disorders (20). In the complex models we assumed that a single locus affects both mean liability to illness and either sensitivity to the environment or probability of environmental exposure. In fact, evidence from animal systems (21) suggests that different genes can control mean expression of a trait and the sensitivity of that trait to environmental perturbation.

The environment is also conceptualized in an unrealistically simplistic way. Many environmental factors probably affect risk for psychiatric illness. Some of the environmental factors of interest in psychiatric illness, such as psychological aspects of the home environment, may be correlated in relatives for reasons unrelated to gene action. Furthermore, environment may best be viewed in a developmental framework in which the impact of environmental events depends on their time of occurrence.

The incorporation of these many features would produce a more realistic but much more complex model. While simple, the present models provide a reasonable first step in conceptualizing the joint effect of genotype and environment on liability to psychiatric illness.

Illustrations and Implications

In this section we provide several examples of the possible utility of such models in psychiatric research. These models can be used as a context for interpreting results of previous studies of psychiatric illness in which both genetic-familial and environmental factors were measured. For example, in examining the role of genetic and environmental effects on antisocial behavior in an adoption paradigm, Cadoret (3) found a nonadditive interaction between genetic and environmental factors influencing antisocial behavior. The

TABLE 4. Two Studies of the Relationship Between Risk of Illness in Relatives and Environmental Exposure of the Proband

Author	Disorder	Relatives	Relatives of Probands With Protective Environment			Relatives of Probands With "Psychological" Predisposing Environment			Relatives of Probands With "Somatic" Predisposing Environment		
			At Risk	Affected		At Risk	Affected		At Risk	Affected	
				N	%		N	%		N	%
Schulz (22)	Schizophrenia	Siblings	995	83	8.3	359	24	6.7	606	24	4.0 ^a
Pollitt (23)	Depression	Siblings and parents	48	10	20.8	143	27	18.9	160	15	9.4 ^b

^aSignificantly different from risk in relatives of probands exposed to a protective environment ($\chi^2=12.1$, $df=1$, $p<.001$).

^bSignificantly different from risk in relatives of probands exposed to a protective environment ($\chi^2=4.6$, $df=1$, $p<.05$).

mean number of antisocial behaviors for an adoptee with neither genetic nor environmental risk factors, genetic risk factors only, environmental risk factors only, and both risk factors were, respectively, 1.1, 1.3, 1.9, and 4.5. These results are what would be predicted if genes were influencing both mean liability to antisocial behavior and the sensitivity of an individual to the pathogenic aspects of the environment. Similar results have been reported by Cloninger et al. (2) for severe forms of alcoholism.

One prediction of the additive model is that risk for illness will be consistently less in relatives of probands who become ill in a predisposing environment than in relatives of probands who become ill in a protective environment. Under nearly all circumstances the two other basic models predict the opposite. Table 4 presents results from two family studies, one of schizophrenia (22) and one of depression (23), in which the risk of illness in relatives was classified as a function of the environmental exposure of the proband. In both studies two putative predisposing environments were identified, consisting of, respectively, psychological and somatic stress. The results of the two studies were quite similar. The risk of illness in the relatives of probands exposed to a protective environment and of probands exposed to a "psychological" predisposing environment did not differ. However, the risk was significantly lower in relatives of probands exposed to a "somatic" predisposing environment. These results are consistent with the hypothesis that genetic (or familial) factors, at least in part, interact additively with somatic environmental stress to determine liability to both schizophrenia and depression. If genes (or other familial factors) were acting only to influence sensitivity to somatic environmental stresses or only to influence probability of exposure to such stress, the pattern of illness in relatives should differ from that found. Furthermore, these studies suggest that psychologically stressful environments do not appear to substantially alter liability to either of these disorders.

These models can be used as a basis for power analyses that will permit an estimation of the sample sizes needed to detect environmental effects on liability to illness. For example, with the parameters of the example of the additive model and the noncentral chi-square distribution (24), table 5 was constructed to show the sample sizes needed to show a difference in

TABLE 5. Effect of Proportion of Variance in Liability Due to the Identified Environment on Sample Size Needed to Detect a Difference in Relatives' Risk of Illness as a Function of the Environmental Exposure of the Proband

Percentage of Variance Due to the Environmental Factor	Sample Size Needed ^a	
	Monozygotic Co-Twins	Siblings
5	514.7	2,803.2
10	231.9	1,207.5
20	102.7	519.8
30	64.2	341.3
40	48.3	236.8
50	40.0	198.7

^aTo detect a significant difference at $p<.05$ in the risk of illness between relatives of probands from a protective environment and relatives of probands from a predisposing environment 80% of the time, using the parameters from the additive model (table 1) and assuming that the probands are equally divided into the two groups and that each proband has one relative.

risk of illness between relatives of probands from a protective environment and relatives of probands from a predisposing environment as a function of the proportion of variance due to the environmental factor. Two results are particularly worthy of note. First, when the environmental factor accounts for less than 10% of the variance in liability, the sample sizes required to detect its effect with this analytic approach will be very large. Second, monozygotic twins are much more informative than siblings for such analyses. In this parameter set one monozygotic co-twin provides as much information as approximately five siblings.

These models also have important implications for the selection of subjects for biologic research in psychiatry. If the biologic marker under investigation is a reflection of the genetic contribution to the liability to illness, then the environmental status of the affected individuals who are studied will have a major impact on the probability of detection of such a marker. For example, assume that the effects of genotype and environment are additive and the biologic researcher is trying to detect the gene product of the A allele. With the parameters used in table 1 the researcher would be far better off studying individuals who became ill in a protective environment (where 74.9% of them will have at least one A allele) rather than those who

became ill in a predisposing environment (where only 48.4% of them will have at least one *A* allele). Substantial differences in the genotypic distribution of affected individuals as a function of their environmental exposure are also found with the other simple models (tables 2 and 3).

Lastly, these models for the joint effect of genotype and environment on liability to psychiatric illness can be incorporated into more sophisticated genetic techniques, such as complex segregation analysis. This analytic method attempts to detect the effects of single loci on liability to illness by an examination of the distribution of illness within pedigrees. The results of simulation studies suggest that when the environmental status of relatives is known, segregation analysis has considerable power for detecting both the additive effect of genes and environment and genetic control of sensitivity to the environment (12). Furthermore, ignoring the joint effects of genotype and environment when they exist can lead to serious errors of inference.

CONCLUSION

This article had two major goals. The first was to demonstrate that genetic and environmental risk factors for psychiatric illness can interact in potentially subtle ways. The second goal was to show that these interactions, albeit with some simplifications, could be rigorously expressed in simple models that could generate clear, testable predictions. It is our conviction that a complete understanding of the etiology of most psychiatric disorders will require an understanding of the relevant genetic risk factors, the relevant environmental risk factors, and the ways in which these two risk factors interact. Such understanding will only arise from research in which the important environmental variables are measured in a genetically informative design. Such research will require a synthesis of research traditions within psychiatry that have often been at odds with one another in the past. This interaction between the research tradition that has focused on the genetic etiology of psychiatric illness and that which has emphasized environmental causation will undoubtedly be to the benefit of both.

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APPENDIX 1. Mathematical Aspects of Models of the Joint Effect of Genotype and Environment on Liability to Psychiatric Illness

For a fuller treatment of the specific models see the 1984 article by Eaves (12). General principles of biometrical genetics have been reviewed by Mather and Jinks (13). In all models presented in this report the probability of illness (*P*) is a logistic function of liability to illness (*L*), calculated as

$$P = \frac{1}{1 + e^{-L}}$$

The models are expressed in terms of liability because this variable can vary from minus to plus infinity, while probability of illness can only vary between 0 and 1. Defining models in terms of probability would be very cumbersome.

For the additive model *L* is in turn a function of four parameters: *m*—the midhomozygous value, *d*—the additive genetic deviation, *h*—the heterozygous genetic deviation, and *e*—the deviation due to the environment. In the additive

model liability is simply the sum of the genetic and environmental deviations. For example, for an *AA* individual in a *predisposing environment* L would equal $m+d+e$ and for an *aa* individual in a protective environment L would equal $m-d-e$ (see figures 1 and 2).

With genetic control of sensitivity to the environment the relationship between the genetic and environmental deviations becomes multiplicative. That is, the genetic deviation now modifies the environmental deviation. The full form of this relationship for an *AA* individual in a predisposing environment would be

$$L=m+e(m_g+d)$$

where m_g is the midhomozygous position for the genetic modification of the environmental effect. This model is simplified by assuming that m_g equals 1, h equals 0, and d is less than or equal to 1. The second assumption means that the genetic control of sensitivity to the environment is assumed to be completely additive (e.g., the heterozygote is exactly midway between the two homozygotes). The third assumption means we assume that liability in the predisposing environment is always greater than or equal to liability in the protective environment. If d exceeded 1, then with the *aa* genotype liability in the protective environment would exceed that found in the predisposing environment. These assumptions reduce the formulae to those seen in figure 3. For example, the previous equation reduces to

$$L=m+e+de$$

With genetic control of environmental exposure the liability to illness is independent of genotype and is simply $m+e$ in the predisposing environment and $m-e$ in the protective environment for all genotypes (figure 4). However, the

probability of exposure to the predisposing environment is now a function of genotype. For the genetic control of environmental exposure we now have a new midhomozygous position, m' , and d and h reflect the additive and dominance genetic deviations altering the probability of exposure to the predisposing environment.

The model for the genetic control of both mean liability to illness and sensitivity to the environment can be expressed in several ways. The full model for an *AA* individual in a predisposing environment would be

$$L=m+d+e(m_g+d_g)$$

where m_g and d_g refer to the midhomozygous position and additive genetic effect on sensitivity and m and d refer to the midhomozygous position and the additive genetic effect on mean liability. For our treatment we have simplified this model to assume that $m_g=d_g=1$ and $h_g=0$. Therefore the genetic effects on sensitivity for the *AA*, *Aa*, and *aa* genotypes reduce to 2, 1, and 0, respectively, as seen in figure 6. The previous equation then reduces to

$$L=m+d+2e$$

The model for the genetic effects on mean liability and probability of environmental exposure is simply a combination of the two simpler models. An individual with an *AA* genotype exposed to a predisposing environment has a liability of $m+d+e$, but in addition, his probability of exposure to that environment is $m'+d'$ (figure 6).

The risk of illness in monozygotic co-twins and siblings is calculated by the ITO matrix method outlined by Li (14). All of the models have been incorporated into interactive computer programs written in BASIC by one of us (K.S.K.) and are available on request.