

E. JUULIA PAAVONEN
M.D., Ph.D., M.Sc., Senior
Researcher
National Institute for Health and
Welfare, Unit for Mental Health
Promotion

TYTTI SOLANTAUS
Docent, Research Professor
National Institute for Health and
Welfare, Unit for Mental Health
Promotion

TIINA PAUNIO
Docent, Psychiatrist, Senior
Researcher
National Institute for Health and
Welfare, Chronic Disease Prevention
Unit, HUS,
Department of Psychiatry

PEER-REVIEWED



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On the origin of psychiatric disorders: An interplay of genetic and environmental factors

- Family, adoption, and twin studies have shown that the inheritance of psychiatric disorders reflects both genetic and environmental factors and their dynamic interaction.
- Environmental factors can affect gene expression, and genetic variation in turn has an impact on the type of environment where an individual lives and how he or she reacts to different environmental factors.
- Thus, psychiatric disorders would not appear to have universal heritability, but heritability estimates are specific to the particular study populations and their characteristic environment. In the end, the story of any individual is always unique.

Epidemiologic studies have shown many risk factors causing predisposition to psychiatric disorders, but the fundamental mechanisms underlying such disorders are not well known as yet. Factors affecting the development of psychiatric disorders appear to form a complicated network where genotype, environment, culture, events in life, and psychosocial factors are in dynamic interaction with one another. This interdependence is complex, as the same disease can develop through many different mechanisms and, by contrast, the same risk factors can give rise to many different disorders. Could this process be placed under the loupe to examine more closely what sort of cellular mechanisms are behind this dialogue between biology and environment? Our aim in this review article is to describe what is known about the interaction between genetic and environmental factors influencing the development of psychiatric disorders.

Genes alone explain only a part of the risk

Family, twin and adoption studies have shown that psychiatric disorders often run in the family (1,2). Children of parents with a history of depression, for example, have a threefold risk of developing some mental disorder by the age of 35 (3). The risk is still greater if depression has occurred in several generations: as many as two out of three offspring will develop depression before long (4). On the other hand, de-

pression may skip generations; a history of depression in a grandparent is associated with depression in the child even when the parents have not been diagnosed with depression (5). Genetic factors would thus appear to be involved in the disease process.

In twin studies, the weight of genetic factors is examined by comparing the similarities between monozygotic and dizygotic twins. If monozygotic twins with nearly identical genomes resemble each other more than dizygotic twins sharing an average of half of their genome, genetic factors would appear to regulate the phenotype. On the other hand, if the risk is equally high for identical and fraternal twins, environment must play more of a role as determinants. According to twin studies, genetic factors are of great significance in schizophrenia and bipolar affective disorder but of less significance in depression. Meta-analyses suggest that genetic factors explain about 81% of the phenotype variation in schizophrenia (6) and 85% of that in bipolar affective disorder (7) but only about 37% of the variation in depression (8). Estimated heritability, however, says little about the probability of developing a disorder; in the case of bipolar affective disorder, for instance, concordance is only 43% even for monozygotic twins and only 6% for dizygotic twins (9).

Molecular genetic studies proper have produced variable data on the mechanisms underlying psychiatric disorders. No single risk

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genes appear to be decisive for the risk of developing such disorders even at the population level (10). Genome-wide association studies have not usually shown any clearly significant connection between genetic factors and psychiatric disorders even though genome-wide surveys of hundreds of thousands, or even millions, of base variations are often made in such studies (11). A recent European study, for instance, included more than 1,400 families with ADHD, but none of the more than 600,000 base variations tested for showed a statistically significant association with ADHD (12). Equivalent studies on the heritability of schizophrenia showed a significant association only when three extensive projects were combined and the number of patients analyzed exceeded 8,000. The most significant association area was found in the short arm of chromosome 6, in the area coding the immune system and histone proteins (13,14).

The high number of genetic variants to be tested also presents a problem for genome-wide association studies. It is difficult and sometimes all but impossible in practice (e.g., in the case of rare diseases) to collect such large patient materials. A genuinely positive finding can easily be masked by some chance erroneous signal and, on the other hand, large materials increase the risk of false positive findings (11). Of genetic variants affecting the risk of disease, it is generally possible to detect only those that are relatively common in the population. Nevertheless, if rare polymorphisms increase the risk of disease more than common risk polymorphisms, their significance at the individual level may be high. In a multinational research project, for example, three very rare chromosome deletions were found to be associated with schizophrenia. Even though they are of little importance at the population level, they have a significant effect on the disease risk of individuals (15). To cover the whole spectrum of risk factors, linkage and association studies focusing on high-risk families are therefore needed.

Such studies have identified many candidate genes increasing the risk of psychiatric disorders. Numerous genes are associated, e.g., with bipolar affective disorder (16) or depression (17), while the same genetic factors may be associated, e.g., with both depression and anxi-

ety disorder (18) or with both bipolar affective disorder and schizophrenia (19). However, results from various materials vary and single genes do not appear to explain much of the phenotype. The data currently available do not allow assessment of the risk of disease for any individual because when the risk ratio is close to one, most of those with high genetic risk potential never fall ill. Psychiatric disorders are polygenic, develop by heterogeneous mechanisms, and show complex heritability.

Twin studies also involve certain basic challenges. There has been considerable variation in estimated heritability depending on the study population, the period of time, and the indicators applied. The estimated heritability of schizophrenia, for example, has ranged from 25% to 90% (6). Environmental factors often interpreted as common in twin studies, such as parenthood or conflicts within the family, may affect twins differently owing to such factors as temperament. Heritability estimates may also be influenced by common environmental factors of this sort, although the effect of such bias has been thought to be negligible (1,20,21).

The growth environment, too, can influence the role of heredity during development. For example, a Swedish twin cohort found that the heritability of regular smoking among women increased with year of birth; the estimated heritability was low among those born before the year 1925, whereas among women born in 1940 or later it was as high as among men (63%) (22). Thus, genetic risk potential may not be manifested in a restrictive environment (the availability of tobacco). Therefore, estimates based on classic twin studies should always be considered specific to the material, the period of time, and the study design (23).

Adoption and family studies

Adoption studies strive to differentiate risks associated with the environment from those associated with heredity by comparing the risk of psychiatric disorder mediated by biological parents in relation to disease risk among adopted and non-adopted children. If adoption does not influence disease risk, the risk would appear to be mediated by biological routes. If, by contrast, the disease risk falls to the basic level as a result of adoption, the risk would ap-

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pear to be mediated primarily through the environment. Study findings clearly indicate that positive disease history in a biological parent increases disease risk in the offspring regardless of adoption. However, the effects of genes and environmental factors are not independent of each other. For instance, antisocial personality disorder in a biological parent increased the adopted child's aggressiveness and risk of conduct disorder, particularly in adoptive families with social problems. On the other hand, an unfavorable adoptive environment affected the risk of antisocial personality disorder only when there was also a biological predisposition (24). Similar results were obtained for a Finnish material: the genetic risk of schizophrenia inherited from a biological parent is manifested particularly in adoptive families with deviant communication models (25).

According to a recent adoption study, maternal depression significantly increases the risk of psychiatric disorder in both biological offspring and adopted children (26), which suggests that environmental factors play a central role in the disease process. It is thus evident that the 'inheritance' of psychiatric disorders from one generation to another also reflects unfavorable environmental factors associated with the parent's psychiatric disorder. Aside from the biological predisposition, children of parents with psychiatric disorder often inherit many social risk factors (such as financial problems, unemployment) and a family atmosphere that may increase the risk of psychiatric disorder. Issues such as negative cognitions in depressed parents and interaction involving other problems may contribute to the development of depression (27). Families of depressed adolescents are more discordant, more rejecting, and less encouraging than other families (28).

Interaction between the environment and genes in the prevalence of psychiatric disorder

Adoption and family studies have offered a natural experimental design for investigating the interaction between genes and environmental factors; molecular genetic research, too, has recently striven to determine how environmental factors modify the effects of genes. In their pio-

neering study on interaction between genes and environmental factors (G x E), published in 2002, Caspi and coworkers reported that the significance of maltreatment in childhood depends on the type of the gene coding the monoamine oxidase A (MAO-A) enzyme (29). This result has subsequently been confirmed by other studies (e.g., 30) but conflicting findings have also been reported. On the basis of meta-analysis, however, there is reasonable evidence of such G x E interaction (31).

The risk of depression, too, may depend on interaction between genotype and environmental factors. The protein responsible for serotonin reuptake in the synapse is called serotonin transporter. The activity of the 5-HTT gene regulating the coding of serotonin transporter is regulated by promoter polymorphism (short/long allele, "s/l"), which is not directly associated with risk of disease. However, it may be of significance for the order in which stressors affect the risk of disease. In another study by Caspi and coworkers, unfavorable life events added to the risk of depression, particularly in s allele carriers (32). This finding has been confirmed in a few other studies, but negative and contradictory findings have also been reported. A few review articles provide excellent summaries of research into this area (33,34,35), and on the basis of a recent meta-analysis, there is insufficient evidence of interaction (36). Interaction studies have been criticized for insufficient power, publication bias, heterogeneous statistical methods, and insufficient control of intervening factors (37). Even though epidemiologic research has revealed numerous factors now known to protect against psychiatric disorder (38), these have hardly ever been considered in G x E studies. To give one example, positive and not overly controlling interaction between the parent and the adolescent predicts a good outcome even when the mother suffers from depression (39). It must still be remembered that transmitter metabolism can be affected by various genes and within a gene by its polymorphism, such as the base change affecting allele activity at the center of the length polymorphism of the serotonin transporter. In addition, events during the development of the central nervous system may have a permanent effect on subsequent transmitter kinetics (40). Among rhesus

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monkeys, for example, the s allele of serotonin transporter was associated with reduced serotonergic activity only in animals brought up in a stressful environment (41).

In addition to the above examples, numerous other possible G x E effects have been reported in the field of psychiatry, but most of these are individual findings on the basis of which it is hard to draw clear conclusions (Table 1). Findings are based on highly varied symptom indicators, and the environmental factors analyzed vary widely from one study to another. Some findings may be of clinical significance for treatment response (42). For example, the FKBP5 gene (FK 506 Binding Protein 51) regulating the responsiveness of the glucocorticoid receptor has been reported to affect the response to SSRI treatment in patients with depression (43).

How does the environment affect genetic risk?

As was mentioned above, genes and environmental factors may interact, but by what mechanism do environmental factors modify the risk of diseases? In the statistical sense, cause-effect relationships can be studied most effectively in an experimental design. Animal studies have shown that genetic variants increasing risk behavior manifest themselves specifically in the presence of unfavorable environmental factors. The results obtained by Michael Meaney and his research group concerning the effects of maternal care on stress response in rat offspring have become all but classic (44). Active maternal care during the first ten days of life permanently reduced stress reactions in the offspring (45). The effect was mediated through hippocampal glucocorticoid receptors: maternal care increased their expression, alleviating stress responses even in adulthood (46). This phenomenon was explained by reversed methylation in the area regulating the glucocorticoid receptor gene: detachment of the methyl group attached to cytosine facilitates the binding of transcription factors to the regulating area, which leads to gene expression (47). This is an epigenetic regulatory mechanism, which affects the activity of a gene without affecting the gene sequence (48). Environmental factors may thus affect gene expression and thereby individual behav-

ior and its regulation.

So far, no such detailed molecular level mechanism has been described for humans. However, abnormal GABA-A gene methylation has been found in post mortem examinations of suicide victims, and it has been speculated that this may reflect long-term effects of depression (49). Even though epigenetic features appear to be hereditary to some extent (48), the level of gene methylation has been shown to vary with time in individuals and even between monozygotic twins, which may suggest that the environment plays a central role in the regulation of gene expression (50,51). The environmental factors with which the observed differences in methylation are associated in humans remain to be seen. It would appear, however, that traumatic experiences in early childhood affect the function of the HPA axis in humans as well, by sensitizing the neuroendocrine stress response and weakening compensatory biological mechanisms protecting against stress (52), which could well be a phenomenon mediated through epigenetic mechanisms.

Is the environment independent of genes?

Interaction between the environment and the individual has traditionally been considered as acting only one way, from the environment to the individual. But genes also affect the individual's external world and the individual's psychosocial environment (21,53). This phenomenon is called gene-environment correlation (rGE), a name emphasizing that environmental factors are not necessarily independent of the effects of genotype. Interdependence between environmental factors and genes may be passive (e.g., the environment where a child is brought up reflects the parents' genotypes), evocative (e.g., a tendency towards depression in one spouse provokes marital discord) or active (e.g., temperamental characteristics affect the type of environment sought by the individual). Thus, the exposure of individuals to different environmental factors is not totally random (21,54); rather, genetic factors affect the susceptibility of individuals to, for instance, certain risky environments.

As small children develop in interaction with their environment, parents play a central role in the psychosocial development of their chil-

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dren. Developmental psychology research has shown that secure attachment is an important factor mediating normal psychobiological development. Attachment as such would not appear to be genetically mediated (55), but cer-

tain genetic features in a child may make the child more vulnerable to unfavorable environmental factors. For example, an allele of dopamine receptor D4 combined with abnormal early care would seem to predispose to

**TABLE 1.
G x E studies.**

Monoamines	Gene	Environmental factor	Disorder/Feature	Reference (positive finding)	Reference (negative finding)
MAO-A	MAO-A	Childhood trauma	Conduct disturbance	29, 30, 67, 68, 69‡, 70, 31, 71, 72	73, 74
		Maltreatment	Antisocial symptoms	75	
Serotonin transmission	SLC6A4	Childhood trauma	Depression, anxiety, somatic symptoms, suicide attempts	70, 76, 77	
	SLC6A4	Stress or stressful life events	Depression	32, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89*, 90*, 91*	93, 94
	SLC6A4	Stress	Anxiety	95	
	SLC6A4	Stressful life events, family relationships	Intoxicants	92, 96	
	5HT2A 5HT2A	Nurturing Residential area	Depression Depression	57 97	
COMT	COMT	Low birth weight	Antisocial behavior in ADHD	99	
	COMT COMT/SRT	Use of cannabis Stressful life events	Psychosis Affective syndrome	100 83	
	COMT	Stress	Psychosis	101	
Dopamine transporter	DAT1 DAT1	Parenting Maternal alcohol consumption during pregnancy	Depression ADHD	102 103	
	CRHR1 FKBP5	Trauma Trauma, maltreatment in childhood	Depression PTSD	104 105, 106	
Nerve cell plasticity	BDNF	Childhood trauma	Depression, cognition	107, 98, 81	
Fatty acid metabolism	FADS	Maternal alcohol consumption during pregnancy	ADHD	108	
	FADS2	Breast-feeding	IQ	109	
	APOE	Childhood trauma	Cognition	98	

* Partly positive result, ‡ association in the opposite direction

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TABLE 2.

Challenges facing psychiatric genetics (110).

CHALLENGES ASSOCIATED WITH THE MEASUREMENT OF DEPENDENT VARIABLES

Differences in measurement methods lead to variation in results and make comparison and interpretation difficult

The dependent variable can be, e.g., a disorder according to a diagnostic classification or a symptom score or an endophenotype

The dependent variable can be measured from data obtained by interview or questionnaire or from registers

CHALLENGES ASSOCIATED WITH THE MEASUREMENT OF GENETIC FACTORS

Epigenetic factors or events occurring during development may affect the function of genes but are rarely taken into consideration

CHALLENGES ASSOCIATED WITH THE MEASUREMENT OF ENVIRONMENTAL FACTORS

Measurement is often imprecise and therefore does not necessarily provide reliable results

Often retrospective (risk of recall bias)

Several informants are seldom used (risk of reporting bias)

The form, duration, or severity of trauma is seldom considered

The individual's experience of the significance of various risk factors may ultimately be decisive

CHALLENGES ASSOCIATED WITH THE CONSIDERATION OF CONFOUNDING FACTORS

There is great variation in the consideration of comorbidity, which makes it difficult to compare results

Protective factors may affect the risk of disease but are seldom considered

CHALLENGES ASSOCIATED WITH INTERPRETATION OF THE RESULTS

Small materials increase the possibility of random findings and make it difficult to consider several factors concomitantly

A statistically significant association may signify a true causal relationship but may also be causally insignificant or may represent a random finding

disorganized attachment (56), and serotonin receptor (HTR2a) polymorphism may affect the receptiveness of the infant to good early nurturance (57). Problems with regulation of conduct in children, too, are expressly related to genetic factors (dopamine D2 receptor gene DRD2), whereas the mother's sensitivity is not associated with her DRD2 genotype (58).

In a child's growth environment, however, interaction between genes and the environment is more complicated than this, for it reflects the genetic characteristics of both the parents and the child (58). A recent study revealed that negative features in parenting were more common in cases where the mother showed certain polymorphism of the dopamine transporter (DAT1), but that problems in interaction related to the maternal DAT1 allele were emphasized in cases where the child also showed problems with self-regulation (59). Likewise, problems in parental expression of emotions seemed to in-

crease the severity of ADHD symptoms precisely in children with genetic risk potential (60). Similar observations have been made in adoption studies: the more aggressive and hostile the behavior of the adopted child was, the more severe and less nurturing the behavior of the adoptive parents became (61). Thus the family environment may, at least to some extent, depend on the child's specific characteristics and regulation of conduct. This therefore presents an example of the evocative correlation model described above.

On the other hand, depending on the child's congenital temperamental characteristics, good outcomes may require different types of parenting. Judged by the development of a conscience, gentle nurturing, for example, had a favorable effect only on children with fearful temperament, and a clear and firm approach worked better for fearless children (62). What it takes to provide 'good' and protective parent-

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Financial ties:

Juulia Paavonen and Tytti Solantausta have not reported any financial ties. Tiina Paunio has made presentations at events organized by pharmaceutical companies and participated in a congress abroad at the expense of a pharmaceutical company.

ing may therefore depend essentially on the child's characteristics and temperamental features - and thus also on the child's genotype (63).

However, as yet there is no sound research-based evidence of how early care affects the risk of disease in adulthood. In small research materials, secure attachment has been found to modify the 5-HTT-mediated risk of reacting in a stress test (64), and good early care may eliminate the impact of antenatal stress during the first years of life (65). Many other longitudinal studies have been based on such limited materials that their power has not been sufficient to prove the advantages of good early interaction over time.

Final remarks

There are many methodological problems involved in studying the heritability of psychiatric disorders (Table 2). Although the use of official diagnostic criteria ensures comparability between various studies, it can also lead to problems, since the background of any disease group may be heterogeneous and, in turn, various groups of diseases may involve overlapping features based on the same causal mechanisms. Sticking to DSM or ICD classifications may thus prevent finding the true etio-

logical factors. Bipolar affective disorder, for example, probably shares some predisposing genes with both schizophrenia and other mood disorders. In addition to diagnostic groups, etiological studies should therefore pay attention to symptoms and hereditary features causing predisposition to disease, so-called endophenotypes (66).

Current research supports the idea that the manifestation of risk potential for psychiatric disorders often requires unfavorable environmental conditions. Psychiatric disorders therefore lack unequivocal heritability even at the population level; rather, estimated heritability is always specific to a certain population and its characteristic environmental factors (54). Even though at their best estimates may explain the origins of disorders at the population level, profiling of mechanistic paths at the individual level is challenging if not impossible. Data on the interaction between genes and the environment emphasize the importance of preventive work. Even the strongest family history is not decisive; rather it indicates groups where active measures should be taken to reduce environmental risks, to strengthen protective factors, and to provide appropriate treatment at an early stage of the disease process. ■

■ ENGLISH SUMMARY

On the origin of psychiatric disorders: An interplay of genetic and environmental factors

Psychiatric disorders run in families. Family, adoption, and twin studies have shown that the intergenerational transfer of psychiatric disturbances reflects both genetic and environmental factors and their dynamic interplay. Environmental factors can affect gene expression, and genes in turn have an impact on how an individual reacts and behaves in different environmental conditions. Thus, psychiatric disturbances do not have universal heritability, but heritability is conditional to the particular study population and its environmental factors. This has implications for prevention of the intergenerational transfer of psychiatric disorders and underlines the need to reduce environmental stressors in families with parental mental disorder.

TIINA PAUNIO

M.D., Ph.D.
Public Health Genomics Unit and Institute for Molecular Medicine FIMM, National Institute for Health and Welfare, Biomedicum

E. JUULIA PAAVONEN, TYTTI SOLANTAUSTA