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Genes, stress, and depression

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Abstract

A relationship between genetic makeup and susceptibility to major depressive disorder (MDD) has long been suspected on the basis of family and twin studies. A metaanalysis of reports on the basis of twin studies has estimated MDD's degree of heritability to be 0.33 (confidence interval, 0.26-0.39). Among families exhibiting an increased prevalence of MDD, risk of developing the illness was enhanced in members exposed to a highly stressful environment. Aberrant genes can predispose to depression in a number of ways, for example, by diminishing production of growth factors that act during brain development. An aberrant gene could also increase or decrease a neurotransmitter's release into synapses, its actions, or its duration of activity. The gene products of greatest interest at present are those involved in the synthesis and actions of serotonin; among them, the serotonin-uptake protein localized within the terminals and dendrites of serotonin-releasing neurons. It has been found that the V_{max} of platelet serotonin uptake is low in some patients with MDD; also, V_{max} is highly correlated in twins. Antidepressant drugs such as the selective serotonin reuptake inhibitors act on this uptake protein. The specific genetic locus causing serotonin uptake to be lower in some patients with major depression involves a polymorphic region (5-HTTLPR) in the promoter region of the gene for the uptake protein. The gene itself exists as several alleles, the short "S" allele and the long "L" allele. The S variant is associated with less, and the L variant with more, of the uptake protein. The effect of stressful life events on depressive symptoms in young adults was found to be significantly stronger among SS or SL subjects than among LL subjects. Neuroimaging studies showed that people with the SS or SL alleles exhibited a greater activation of the amygdala in response to fearful stimuli than those with LL. It has been reported recently that mutations in the gene that controls serotonin synthesis in the human brain (tryptophan hydroxylase) also predispose to mood disturbances. It may be asked whether people who lack a psychiatric history should be advised to avoid stressful environments if they are found to carry the SS or SL alleles.

1. Genetic influences on susceptibility to major depression

Genes have not been shown to cause major depressive disorder (MDD) in the same sense that a single defective gene causes people harboring that gene to develop Huntington's disease, regardless of how serene their environment may be. However, as described below, genes clearly can be a risk factor for developing depression, increasing the likelihood that severe environmental stresses will precipitate the onset of this disease [1].

A relationship between genetic makeup and susceptibility to MDD has long been suspected on the basis of the existence of families devastated by multiple suicides (a behavior that may not always be associated with MDD [2], but is nonetheless considered a major risk in depressed individuals). However, studies performed during the past decade on twins and on specific brain proteins involved in neurotransmission have raised the probability of a genetic contribution to MDD well beyond that based simply on clinical anecdotes. And it can be anticipated that future studies on the basis of our knowledge of the human being's genetic code will soon relate particular substitutions of individual bases in a person's DNA to particular MDD syndromes, which differ in the extent to which that person exhibits such classic depressive symptoms as mood disturbances, psychomotor retardation, sleep disorders, fatigue, or thoughts of death [3]. The fact that variations in genetic makeup can be phenotypically "silent," producing no signs of MDD except after people find themselves in an unusual (stressful) environment, is reminiscent of the consequences of having a great athlete or violinist for a parent: The relevant genes, if transmitted, can increase the likelihood that the offspring will also exhibit similar gifts, but only if they practice assiduously.

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1.1. Twin studies

At least 5 reports on the basis of twin studies, describing 11 subject samples, have been published demonstrating that the etiology of major depression (MDD) has a significant heritable component [4]. A metaanalysis of these studies [5] estimated MDD's degree of heritability at 0.33 (with a 95% confidence interval of 0.26-0.39). Heritability was greater in women with MDD than in men [6] (as is the prevalence of MDD in general), and was also most likely to cause phenotypic expression among individuals who lived in environments that provided diverse types of experience, particularly when such environments included highly stressful life events [1,7]. Expression of MDD's heritability is also influenced by the family environment; thus, "parental coldness" was found to be associated with a 38% increased risk for developing this disease [4]. Familial dysfunction and genetic predisposition could interact to promote MDD in several ways; for example, an errant gene affecting brain function might—as proposed below—make the individual more vulnerable to environmental stresses, or by impairing the child's temperament, might make life in the family intrinsically more stressful.

Aberrant genes could also predispose to depression, for example, by affecting the numbers of particular types of neurons or the numbers of synapses the neurons make, perhaps by diminishing the production of growth factors that act during brain development or thereafter. This type of mechanism might explain the observation—demonstrated in twin studies—that individuals with a smaller-than-normal hippocampus are more likely than others to develop posttraumatic stress disorder [8].

1.2. Neurotransmission as a locus for gene-based susceptibility to depression

One possible way that aberrant genes could predispose to depression is by affecting neurotransmission: the aberrant protein that the gene caused to be produced might increase or decrease a neurotransmitter's release into synapses, or its actions, or its duration of activity. For example, a faulty gene that diminished the activity of the protein that mediates γ-aminobutyric acid's reuptake could thereby unduly suppress the release of norepinephrine or dopamine from the next neuron in a synaptic chain. Or a faulty gene for choline acetyltransferase or the M1 muscarinic receptor could impair a hippocampal circuit that normally is activated by the cholinergic septal input. The prime candidates for such neurotransmitters are those on which antidepressant drugs are known to act, specifically the monoamines serotonin and norepinephrine.

1.3. The serotonin-uptake gene and the susceptibility to depression

The gene products currently being explored most extensively as possible mediators of the genetic contribution to MDD are proteins involved in the synthesis and actions of serotonin—particularly the serotonin-uptake protein, which is localized in platelets and within the terminals and dendrites of serotonin-releasing neurons. Gene-based depression-related disturbances in the enzymes needed for serotonin biosynthesis and in various serotonin receptors and metabolizing enzymes, such as monoamine oxidase (MAO), are also being described [9].

Interest in the serotonin-uptake protein as a mediator of genetic susceptibility to depression had its origins in the demonstrations by Meltzer et al [10] that the V_{max} of platelet serotonin uptake was low in some patients with MDD, and that this V_{max} was heritable (because it was highly correlated between twins, especially monozygotic twins) [11]. Subsequent studies [12] also demonstrated that the V_{max} for brain serotonin uptake, or that of its analog imipramine, also was low in people with a history of depression. Another correlation suggesting the involvement of the serotonin-uptake protein in MDD was the abundantly documented antidepressant activity of selective serotonin reuptake inhibitor (SSRI) drugs, such as fluoxetine, sertraline, and paroxetine, which act on this uptake protein. There is, of course, a paradox in the observation that low serotonin uptake resulting from a genetic propensity, that is, the 5-HTT-S allele, is associated with a greater likelihood of developing depression, whereas low serotonin uptake caused by taking SSRI drugs is the basis for treating depression. This paradox remains unresolved but could arise from the fact that if a gene depresses serotonin uptake, it does so throughout the individual's lifespan and may therefore have caused permanent changes in the developing brain. On the other hand, if an SSRI drug depresses serotonin uptake, it does so only while the drug is being administered, usually in adulthood when the brain is more fully developed and therefore less subjected to plasticity and to permanent structural-functional changes.

The specific genetic locus that causes serotonin uptake to be lower in some patients with major depression involves a repetitive sequence (a polymorphic region or 5-HTTLPR) in the promoter region of the gene (5-HTT) for the uptake protein [12]. The gene itself is located on chromosome 17q11.2; its protein product, which contains 630 amino acids, has been cloned. 5-HTTLPR exists as several alleles, most commonly a short "S" allele containing 14 repeated elements or a long "L" allele containing 16 such elements. One predominantly North American-European population displayed allele frequencies of 57% for the L allele and 43% for the S allele. The long and short alleles differentially modulate the transcriptional activity of the gene's promoter, yielding differences in the amounts of messenger RNA for the uptake protein, and of the protein itself. The S variant is associated with less of the serotonin-uptake protein, and the L variant with more of this protein [13].

1.4. The serotonin-uptake gene and the precipitation of depression by stress

Perhaps the most compelling evidence presented to date that a genetic lesion—polymorphism in the serotonin-uptake

gene—can affect the likelihood that life stresses will precipitate depression was described in a prospective longitudinal study published by Caspi et al [1]. In this study, data from 847 twenty-six-year-olds, who had been examined at approximately 3-year intervals between ages 3 and 21 as part of a health and development study, were divided into 3 subgroups on the basis of their 5-HTTLPR alleles, that is, those with 2 S alleles (17%), 2 L alleles (31%), or 1 of each allele (51%). It was then determined whether each subject had undergone stressful life events between ages 21 and 26 years (assessed by history), and whether the subject had suffered a major depressive episode in the year before entering the study. "Stressful life events" were assessed using a highly reliable life-history calendar [1] that inquired about 14 types of events (eg, relating to employment, financial status, relationships, housing, or health). Depression was assessed using the diagnostic interview schedule [14]. Thirty percent of subjects had undergone no stressful events in the qualifying period; the others had experienced one or more such events. The frequency of stressful events was unrelated to a subject's 5-HTTLPR alleles, or to sex. Seventeen percent of the study members satisfied criteria for having undergone a major depressive episode during the prior year, and 3% reported suicide attempts or recurrent thoughts of suicide during that year.

The effect of life events on self-reports of depressive symptoms at the age of 6 years was significantly stronger ($P < .02$) among SS or SL subjects than among LL subjects. Moreover, the occurrence of stressful life events predicted the onset of newly diagnosed depression ($P < .001$) or suicidal ideation or attempts ($P < .05$) among SS or SL subjects but not among LL subjects. The timing of the environmental stress had to precede the onset of depression, indicating that the observed interaction between stress and depression did not just mean that the SS or SL subjects suffered from 2 unrelated tendencies, that is, to enter situations where they would encounter stress, and to become depressed. The presence of an S gene also predicted whether childhood maltreatment would be associated with adult depression ($P < .05$). The activity of another serotonin-related protein, the enzyme MAO-A, which had previously been shown to moderate children's sensitivity to maltreatment [9], had no relationship (unlike the S allele) to susceptibility to stress-induced depression.

Caspi et al [1] point out that there is no conclusive evidence that the 5-HTT gene is directly associated with depression per se (eg, "endogenous" depression); rather, the gene's effect is based on the "Gene × Environment" interaction described above. This observation is compatible with findings from studies on mice [15], in which SS or SL animals exhibited greater stress-induced increases in plasma adrenocorticotropic hormone levels than LL animals—and on rhesus macaques—in which rearing in a stressful environment lowered cerebrospinal fluid 5-hydroxyindole acetic acid concentrations among SS but not LL animals [16]. Moreover, neuroimaging studies have shown that people with the SS or SL alleles exhibit a greater activation of the amygdala in response to fearful stimuli than those with LL, but do not exhibit differences in basal amygdala activity [17].

The possibility mentioned above, that mutations in the gene for the enzyme that controls serotonin synthesis in the human brain—tryptophan hydroxylase (hTPH2)—might also predispose to mood disturbances, has recently received strong support from studies by Zhang et al [18]. These investigators examined the frequency of single nucleotide polymorphism in this gene, involving replacement of an arginine molecule (Arg441) with histidine, among 87 patients with unipolar major depression and 219 control subjects. (This polymorphism causes an 89% decrease in serotonin production when it is expressed in PC-12 cells.) Nine of the patients, but only 3 of the control subjects (and none from another cohort of 60 patients with bipolar depression), exhibited this polymorphism. The authors propose that the mutation-induced "... defect in serotonin synthesis may represent an important risk factor for unipolar major depression."

1.5. Some unresolved questions

Do people with the SS or SL alleles actually have less serotonin-mediated neurotransmission than their LL peers, particularly within brain regions known to be involved in mood and anxiety? And when these people become depressed, are they more sensitive to the antidepressant drugs (such as the SSRIs or MAO inhibitors) that amplify serotoninergic neurotransmission? If the findings of Caspi et al are widely replicated, would it then be useful to inform people who lack a psychiatric history whether, on the basis of in vitro studies on their platelets, they carry the SS or SL alleles, and thus should try to avoid stressful environments? Are there also other genes, perhaps unrelated to serotonin, that can enhance an individual's susceptibility to stress-related depression, and if so, are the particular symptoms of such depressive syndromes different from those associated with the 5-HTT gene? Do other genes, perhaps also affecting serotoninergic neurotransmission, predispose to endogenous depression, crippling anxieties, panic attacks, obsessive thinking, or great anger that some people develop in response to severe stresses? Many questions ... but also good prospects for many answers in the next few years.

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