

## Chapter 2

# Genetic Etiology of Illness

**Abstract** This chapter begins with definitions of important concepts in genetics and continues with summaries of genetic influences on personality and behavior. Interactions between heredity and environment are described within the context of the Pathways Model. Genetic factors that create necessary and/or sufficient contributions to the physical and psychiatric disorders that are the focus of this text are emphasized.

**Keywords** Genetics and illness • Heredity and environment • Genotype • Phenotype

### Definitions

Genes are units of inheritance positioned at locations on a chromosome. A gene is a segment of DNA that contains the coding information for a set of protein molecules, made up of linear chains of amino acids. Alleles are alternate forms of a gene. The alleles for a trait occupy the same locus or position on homologous chromosomes and govern the same trait. Traits that are hereditary, such as eye color or blood type, depend entirely on the particular genes that a person inherits. In contrast, traits that are acquired depend on nongenetic factors such as the person's tendency to wear their hair short. Genotype is the associated gene carried by a person; phenotype is the observable feature. In twin studies, when identical or monozygotic twins show the same trait or feature and dizygotic or fraternal twins do not, then genetic influences are implicated. Concordance refers to the similarity between a pair of twins in a particular trait or specific disease. Phenotypes may appear as blends or intermediate expressions determined by multiple genes. For example, skin and hair color are polygenetic (determined by genes at two or more positions on the chromosome), but these genes are also influenced by environmental factors, in addition to observation and learning (Bazzett, 2008). The heritability coefficient is defined as "the proportion of the observable differences measure within a sample of people that are directly attributable to the genetic differences between them" (Jang, 2005).

Race is often considered as a key determinant of health based on the observations that certain diseases occur more frequently in persons from certain parts of the world. But genetic ancestry is more closely correlated with geographic ancestry than with that of racial ancestry, due to immigration and intermarriage (Bamshad, 2005). It is important to remember that studies of “racial” factors rarely have included genetic analysis but instead rely on participants’ self-report of ancestry.

In summary, the genotype (G) plus environment (E) plus GE interactions determines the phenotype (P) (Bazzett, 2008). Epigenetics refers to inherited changes in gene expression associated with mechanisms other than changes in the DNA sequence. Personality, behavior, and most medical and psychiatric disorders result from complicated interactions among multiple genes and environments. A useful way of understanding the interaction between heredity and environment is that the genotype determines the range of possible phenotypes. The phenotype emerges during development and maturation when genes interact with all the environmental factors to which the person is exposed (Rutter, 2006).

## Genetics and Personality

The personality traits that a person exhibits result from a complex blend of genetic and environmental factors that are further sculpted by learning and cultural influences (Yong-Kyu, 2009). Determining the association between a specific polymorphism, such as the variable length of the serotonin transporter gene, and a personality trait is extremely difficult, even with large populations and extensive genetic analysis (Saffron et al., 2005). However, it is instructive to focus on genetic influences on one or two aspects of personality, since enduring characteristics impact behavioral choices, which in turn affect risk for medical and psychiatric illness.

Fear as an inherited trait can serve as a model system to explore inheritance patterns, modification of responses during development, and emergence of anxiety disorders. All animals are born with instinctive fears that are important for survival in their natural environments. The sight and smell of a predator sets into motion certain actions which increase the animal’s chances of survival; these actions are not learned, but are available to the animal as soon as it is physically capable of enacting them (Panksepp, 1998). Similarly, the specific fears that human infants have at birth are necessary to protect them during the early years of life, but the adaptive significance of these fears changes with age (Eaves & Silberg, 2008). The core fears (confinement, isolation, pain) are modified over time as the child experiences different situations without adverse effects. For example, fear of the dark gradually declines during early and middle childhood, as the child’s brain is able to distinguish darkness that is pleasant or comfortable in contrast to unsafe and potentially dangerous darkness. Rates of changes in fear intensity are variable by gender and age. Male adolescents with a greater predisposition to be frightened of strangers and darkness tended to maintain fear responses longer compared to those who had smaller genetic loading (Goldsmith & Lemery, 2000).

Neuroticism is a personality trait characterized by experience of negative emotions, such as anxiety, sad mood, and hostility. There is a significant heritable component to neuroticism, specifically in BDNF (brain-derived neurotrophic factor). A common variant of BDNF is the substitution of the amino acid valine (val) for methionine (met). In a study by Sen et al. (2003), persons who were homozygotes for the met allele had the lowest neuroticism scores, as indicated by the NEO Personality Inventory (Costa & McCrae, 1997). In contrast, the homozygotes for the val allele had the highest scores and the heterozygotes were in between. (If both alleles are the same, the individual is homozygotic, and if the alleles are different, he or she is heterozygotic.) BDNF gene variants may mediate not only the tendency for neurotic personality but also the pathophysiology of the clinical syndrome of depression (Sen et al., 2003). Furthermore, the neuroticism trait has been associated not only with psychological distress but an increased risk of a physical disorder, ulcerative colitis (Charles, Kato, Gatz, & Pedersen, 2008).

## Genetics and Risk

Heredity can increase or decrease risk for pain sensitivity. Finan et al. (2010) studied the experience of pain in women with fibromyalgia. The pain experience and the effects of pain on mood were partially controlled by the catecholamine and opioid neurotransmitter systems and the catechol-o-methyltransferase (COMT) and the mu-opioid receptor (OPRM1) genes. Genetic and psychological analyses showed that women with the met/met genotype had worse mood and more functional impairment on days when pain was severe compared to those women with the val/met variant or the val/val genotype. Similar analyses were conducted on the asp (aspartate) or asn (asparagine) genotype. Patients with the asn/asn allele were less able to focus on any other experience other than their suffering compared to women with at least one asp allele. Diatchenko et al. (2005) also reported on genetic influences on pain sensitivity, by studying variants of genes that control COMT, an enzyme that regulates levels of catecholamines and enkephalins. A high probability of acute jaw pain becoming chronic temporomandibular joint disorder was partially determined by low COMT levels (i.e., relatively high catecholamines in the synapse). McLean (2011) analyzed the contribution of genetically induced pain sensitivity (COMT), the HPA axis, stress, and physical injury. Some, but not all, individuals who sustain a motor vehicle accident and a whiplash injury continue to suffer pain months after the event. Those who report chronic regional or widespread pain were more likely to demonstrate excessive physiological stress responses and the high-risk genetic variant. A summary of research associating candidate genes with variations in perception of experimental pain can be found in Fillingim (2010).

Using a behavior genetic model, temperamental fearfulness, as described earlier, is a moderately strong predictor of later anxiety. When the normal fear responses do not habituate over time during development and instead become exaggerated, the stress hormone cortisol remains elevated, providing a tentative physiological expla-

nation for the behavioral responses. Fearful, shy children develop into adolescents with frequent social anxiety. These teens overreact to common stressors at school and with their peers. Later, as adults, their risk for generalized anxiety disorder and other anxiety disorders is increased (Goldsmith & Lemery, 2000).

The risk for a physical illness, such as hypertension, is also influenced by inheritance and modified by behavior. A group of 500 undergraduate students had their heart rate and blood pressure measured before, during, and after a test in mathematics. Those students who still had elevated blood pressures at the end of the test and were slower to return to baseline BP were those who had two parents with essential hypertension. So these students seemingly were unable to shut off the stress-mediated increases in sympathetic nervous system activity at the end of a stressful situation (Gerin & Pickering, 1995). Thus, the delay in recovery from stress increases the risk for essential hypertension later in life.

Plasminogen activator inhibitor (PAI-1) is a primary inhibitor of the fibrinolytic system, involved in clotting. When this fibrinolytic system is not inhibited to a sufficient extent, then the individual is more likely to demonstrate excessive clotting, increasing the risk for stroke (Yamamoto et al., 2002). Stress-induced changes were found in the expression of the gene responsible for plasminogen activator inhibitor type 1 (PAI-1), linking genetics and risk for a serious cardiovascular event.

## Genetics and Environment

Life experiences and the environment can change the expression of a gene by coding the DNA that controls the function of that gene, not the genetic code itself (Mill & Petronis, 2007). Important studies on mother rats and pups showed that nurturing behavior by the mother increased the resilience of the pups by boosting the expression of the genes that modify release of corticosterone, the stress hormone. This is a good example of epigenetics. When the pups who had been well cared for by their mothers were exposed to restraint stress, they were less agitated. In contrast, the pups who received less licking and grooming by their mothers had fewer corticosterone receptors in the hypothalamus, resulting in deficient feedback and inability to deactivate the stress responses (Rutter, 2006). In human infants, the same principles apply. Neglect and lack of positive attachment figures impairs brain development, leading to lower intelligence, developmental delays, and later difficulties in socioemotional functioning (Perry, 2002).

A more complex interaction between genes and environment is demonstrated by the research that integrated parenting of difficult children with genetic influences, called evocative-environmental correlations (Eaves, Chen, Neale, Maes, & Silberg, 2005). A study of 473 preschool-aged children and their parents showed that children with the A1 allele of the dopamine D2 receptor gene were more likely to develop early-emerging anxious and depressive symptoms. These children also received less positive parenting, which has its own negative effects on mood and behavior (Hayden et al., 2010; Reiss et al., 1995). Further, the A1 allele and its emotional effects appear to elicit less positive parenting.

Caspi et al. (2003) reported that situational stress can lead to depression in some people but not in others, depending on the length of alleles in the serotonin transporter gene. Serotonin is a major neurotransmitter involved in regulation of mood. Individuals with the short allele in the serotonin transporter gene were more likely to become depressed after stressful life experiences. In another study of the transporter gene, medical students were tested for the short/long variant in the same serotonin transporter gene. Those students who experienced multiple stressors and had the two short alleles were the most likely to develop depressive symptoms (Rosen et al., 2010). However, the relationship between genes and environment is likely to be more complicated than a single gene can explain. Meta-analysis of several studies of the serotonin transporter gene and stress (that did not include the medical student study) found no evidence that a single gene variant was responsible for the stress–depression link (Risch et al., 2009).

The controversy about the link between stressful life circumstances and the serotonin transporter gene was further explored by Mueller, Armbruster, Moser, Canli, and Lesch (2011). These authors postulated that age may be the most important modifying variable and indeed showed that the relationships only occurred in younger adults and only when the primary stressful events had occurred during the first years of life.

Some environmental factors, such as physical activity, would seem to be protective against illness, but genetic factors may nullify the potential benefits of the positive behavior. A thought-provoking study of physical exercise in teenaged girls delineated two groups: some teens demonstrated positive effects of exercise on mood, while others did not. The girls who had a BDNF met allele benefited from activity, while girls with the val/val polymorphism gained little advantage with exercise to enhance positive mood. BDNF levels were abnormally low in the blood of depressed teens; the potential for successful treatment was highlighted in the study by Mata, Thompson, and Gotlib (2010). Treatment of teenagers suffering with clinical depression with antidepressants brought the levels of BDNF back to normal and returned mood to euthymia.

## Genetics and Psychiatric Illness

Most of the psychiatric illnesses that have been studied suggest some degree of genetic influence, but even those with high heritability, like bipolar disorder and schizophrenia, are also influenced by the environment. Bipolar disorder is a chronic illness whose prevalence in the general population is about 1%. The heritability of the disorder is approximately 0.8, meaning that 80% of the variance in transmission can be attributed to heredity (Mansour, Monk, & Nimgaonkar, 2005). In identical twins, there is a 50% concordance for schizophrenia, indicating a significant nongenetic contribution. As discussed above, genes linked to disorders may heighten sensitivity to environmental occurrences like stress, suggesting that genetic loading may be a necessary but not sufficient condition for a psychiatric disorder. Overlap also exists between certain disorders (bipolar disorder and schizophrenia) leading to hypotheses about shared susceptibility (Green et al., 2005). Although schizophrenia

and bipolar disorder have been classified as distinct disorders through many revisions of the DSM, molecular genetic studies have highlighted overlapping risk for the psychotic, schizoaffective, and bipolar diagnoses (Craddock & Forty, 2006). In time, probably all emotional disorders will be shown to be polygenic, with each gene contributing only a small percentage to the disordered phenotype.

Studies of the actions of antidepressants are instructive in understanding the molecular pathways mediating unipolar depression, where the genetic contribution is estimated at about 40%. Candidate-associated proteins implicated in mood disorders include the serotonin transporter protein (Ogilvie et al., 1996), the norepinephrine transporter protein, c-AMP responsive element-binding protein (observed in depressed women), and cadherin, a fat-like protein affected by treatment with lithium (Bazzett, 2008). Chronic stress is a significant contributor to worsening mood, implicating the hypothalamic–pituitary–adrenal axis in depression (Bornstein, Schuppenies, Wong, & Licinio, 2006). Further, the expression of BDNF in the hippocampus is reduced by severe and prolonged stress, while in animal studies antidepressants increase BDNF levels (as mentioned earlier) as well as resistance to stress (Lee, Jeong, Kwak, & Park, 2010).

A large-scale study of 2,111 same-sex twins identified four coherent genetic factors: Axis I disorders, Axis II disorders, internalizing disorders, and externalizing disorders (Kendler, Aggen, Knudsen, Roysamb, & Neale, 2011). Distinguishing between Axis I and II disorders relies on differences between problems that are largely episodic and transient in contrast to disorders labeled as “enduring, pervasive, and stable over time” (Sadock & Sadock, 2003). Estimated proportion of the variance attributed to genetic effects (heritability) ranged from a high of 0.60 for agoraphobia to a low of 0.28 for dysthymia in these common Axis I disorders. For the Axis II personality disorders, the highest heritability was 0.50 for antisocial and the lowest was 0.29 for paranoid personality disorder. Support was evidenced, based on genetic analyses for separation of Axis I and Axis II disorders. However, the separation was far from perfect. Two Axis I disorders were in the Axis II internalizing cluster (dysthymia and social phobia), and from a solely genetic viewpoint, social phobia belonged with avoidant personality disorder and dysthymia in an unspecified personality disorder (Kendler et al., 2011).

## Genetics and Physical Illness

Autonomic disorders are debilitating dysfunctions of the sympathetic or parasympathetic nervous systems. One such problem, postural orthostatic tachycardia (POTS), is characterized by increased heart rate upon assuming upright position. Instead of the normal increase in blood pressure and heart rate when these individuals stand up, parasympathetic dominance ensues, dropping the pressure, leading to syncope. Ten percent of individuals are born with low autonomic nervous system tone. The etiology of POTS can be partially explained by a gene defect in the norepinephrine transporter gene, causing reduced clearance at the synapse. More than

normal amounts of norepinephrine leak out of the synapse, and there is reduced reuptake back into the synapse. Sympathetic activation decreases during attempts at changing position from sitting or lying to the upright stance (Shannon et al., 2000). Persons with POTS often experience significant functional impairments in the work, school, and social settings, so the comorbidity with anxiety and mood disorders is not surprising (McGrady & McGinnis, 2005).

The metabolic syndrome consists of the primary disorders: essential hypertension, type 2 diabetes, obesity, and hyperlipidemia. Markers for the syndrome include C-reactive protein (CRP), circulating inflammatory markers, tumor necrosis factor, interleukin-6 (IL-6), PAI-1, or reduced levels of anti-inflammatory substances such as adiponectin (Zimmet, Magliano, Matsuzawa, Shaw, & Shaw, 2005). In a study of Caribbean Hispanic families, the heritability for the metabolic syndrome was 24%; factor analysis yielded two independent factors: the first was lipids, glucose, and obesity, and the second factor was blood pressure. The heritability for factor 1 was 44% and that for factor 2 was 20% (Lin et al., 2005). Although familial aggregation was smaller in European families, all showed heritability (Freeman, Mansfield, Barrett, & Grant, 2002). Family history of diabetes evidenced genetic heterogeneity with linkages to at least four chromosomes (Cheng et al., 2010). Ghrelin is a circulating peptide which stimulates appetite. An association between the ghrelin gene and obesity in adults was identified (Pulkkinen, Ukkola, Kolehmainen, & Uusitupa, 2010). There is also significant overlap among the factors comprising the metabolic syndrome and abnormal autonomic tone, in particular lower heart rate variability (Gehi et al., 2009). Nonetheless, the practitioner should recall that the metabolic syndrome results from genetic predisposition, *in addition to* environmental, personality, and behavioral factors (Maury, Ramsey, & Bass, 2010).

## Genetic Factors in Coexisting Disorders

Reviewing the literature on the role of heredity on mental and physical illnesses immediately draws attention to the multiplicity of interactions among emotional and medical disorders. A few examples highlight this observation. Circadian clock genes are implicated not only in sleep disorders (Cuninkova & Brown, 2008) but in major depression and bipolar disorder (Mansour et al., 2005) and seasonal affective disorder (Hampp et al., 2008). Depressed patients report poorer sleep efficiency, early morning awakenings, and non-restorative sleep (Lamont, Legault-Coutu, Cermakian, & Boivin, 2007). Another common comorbidity is the association between elements of the metabolic syndrome (specifically obesity and diabetes), sleep cycle, and depression (Scott, Carter, & Grant, 2008). Sleep deprivation has been correlated with eating habits, increased appetite, and the current epidemic of overweight American adults (Hamet & Tremblay, 2006). Further, it is postulated that the circadian regulatory system in the hypothalamus and in peripheral tissues is closely aligned with eating behavior, activity schedule, and ultimately with the metabolic networks (Marcheva, Ramsey, Afinati, & Bass, 2009).



## Summary

Knowledge of genetic influences on disease is important, but should not necessarily lead to drastic changes in treatment models. The isolation of a pathogenic gene points to “the beginning of a chain of events leading to the disease.” In mental disorders, this chain of events is likely to be highly complex: not related to a single gene and lengthy in terms of how soon the phenotype will be expressed. Development, aging, and stress in addition to many other environmental influences continuously modify the observable phenotype and the risk for medical and emotional illnesses.

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<http://www.springer.com/978-1-4419-1379-1>

Pathways to Illness, Pathways to Health

McGrady, A.; Moss, D.

2013, XIV, 263 p.,

ISBN: 978-1-4419-1379-1