Review

Biological Psychiatry: Celebrating 50 Years

Genetics of Resilience: Gene-by-Environment Interaction Studies as a Tool to Dissect Mechanisms of Resilience

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ABSTRACT

The identification and understanding of resilience mechanisms holds potential for the development of mechanistically informed prevention and interventions in psychiatry. However, investigating resilience mechanisms is conceptually and methodologically challenging because resilience does not merely constitute the absence of disease-specific risk but rather reflects active processes that aid in the maintenance of physiological and psychological homeostasis across a broad range of environmental circumstances. In this conceptual review, we argue that the principle used in gene-by-environment interaction studies may help to unravel resilience mechanisms on different investigation levels. We present how this could be achieved by top-down designs that start with gene-by-environment interaction effects on disease phenotypes as well as by bottom-up approaches that start at the molecular level. We also discuss how recent technological advances may improve both top-down and bottom-up strategies.

Keywords: Epigenetics, Gene-by-environment interactions, Genetics, Psychiatry, Resilience, Stress

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In psychiatric research, the phenomenon of resilience has gained increasing attention over the past decade because it holds potential for mechanistically informed prevention and intervention. Resilience is defined as the ability to maintain normal psychological and physiological functioning despite exposure to stress and adversity. Active processes that contribute to maintaining homeostasis within a broad spectrum of environmental disturbances likely underlie this phenotype (1). These processes may have a genetic basis and contribute to the resilient phenotype through a cascade of molecular and cellular events that subsequently regulate neural, physiological, and endocrine systems; these ultimately converge to the maintenance of what we consider normal (or adaptive) behavior. The identification of resilience mechanisms and their genetic determinants, however, is challenging both practically and conceptually. Environmental risk factors play a major role in shaping long-term outcomes for mental health and behavior (2). Hence, exploring human genetic variations that reduce disease risk in light of adversity may serve as a tool to identify mechanisms and pathways that promote resilience. This would allow the mapping of moderating factors' effects across levels of functioning, that is, from molecules to systems to behaviors. This approach could identify how mechanisms of resilience manifest across these levels and provide insight into novel targets for prevention and intervention at all levels.

The aim of this review was to illustrate how human studies that investigate gene-by-environment interactions (G×Es) may help to unravel resilience mechanisms. We illustrate how both classical top-down designs that start with G×E effects on disease phenotypes and bottom-up approaches that start at the level of molecular readouts could contribute to our understanding of resilience mechanisms.

G×E MAPPING TO IDENTIFY COMMON MECHANISMS: DIAGNOSES TO INTERMEDIATE PHENOTYPES

Different conceptional frameworks of how genomic determinants moderate environmental risk have evolved over time. Initially, G×E studies were framed within the diathesis–stress model, which posits that cumulative environmental adversity eventually will lead to dysfunction and that genetic (and other biological) variables determine the individual threshold of adversity necessary for dysfunction to occur. Resilience genotypes within this conceptualization heighten this threshold by affecting adversity-related biological changes. This can happen by reducing long-term negative consequences or by enhancing compensating mechanisms. The diathesis–stress model, however, fails to embed the phenomenon of genetic resilience within a more general theory of environmental sensitivity that is independent of the environment's valence (e.g., stressful vs. nurturing). Relatedly, it fails to explain why susceptibility genotypes have not been selected against during evolution. These shortcomings are addressed in newer, evolutionarily grounded concepts such as the match–mismatch and differential susceptibility frameworks that embed susceptibility and resilience genotypes within a unifying theory of general programming susceptibility to environmental influences, be they adverse or positive (3). Differential sensitivity to environmental programming within these

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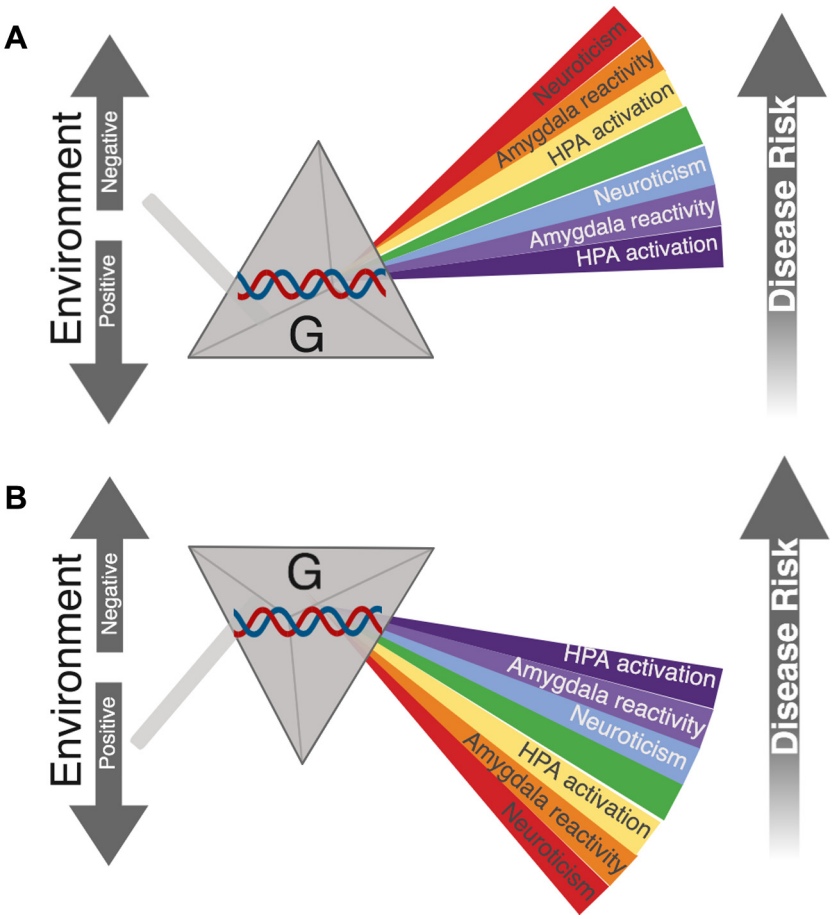

Figure 1. Schematic representation of the concept of resilience and its relationship to gene-by-environment interaction as proposed in this review. **(A)** Situation of high environmental adversity. High adversity is associated with higher disease risk across diagnostic categories. This, however, is not the result of environmental shaping of disease-specific risk factors but rather is mediated through environmental programming of intermediate phenotypes such as hypothalamic-pituitary-adrenal (HPA)-axis functioning, amygdala reactivity, and behavioral dispositions (color beams). The extent of environmental impact on these domains is mediated through genetic determinants such as common gene variants in various genes (G). Here, individuals with less susceptible genotypes (cold colors) show less environmental moderation (or programming) of these domains and hence less increase in disease risk. As such, in this environmental context, they represent a resilient phenotype. The opposite situation is depicted in warm colors. **(B)** Situation of a highly nourishing environment. Here, the less susceptible genotype will lead to more disease risk because the positive environmental influences less shape (or program) the disease risk-conferring intermediate phenotypes toward the low-risk direction. This ambiguous nature of risk and resilience that rests on the notion of more or less environmental programmability is formulated in the framework of differential susceptibility.

conceptualizations can be adaptive or maladaptive depending on the individual's environmental trajectory. Risk versus resilience genotypes may rather reflect high versus low environmental plasticity genotypes (4). This latter, more ecologically valid concept for G×E studies mandates study designs that assess the environment not unidirectionally but rather across the entire spectrum from positive to adverse. Currently, only very few studies have incorporated such multidimensional assessments of the environment, which requires longitudinal designs with complex, multi-informant measures of the environment. Lack of completeness in measurements of the environment across the entire range of development may also contribute to inconsistent findings in G×E studies (5,6). The majority of published studies focus on adversity, often measured at only one or a few developmental time points, which limits our ability to identify whether polymorphisms indeed moderate responses to the complex environment. Despite these limitations, current G×E studies allow us to explore their potential for identifying resilience mechanisms (see Figure 1).

Candidate Gene Strategies

We first explore how candidate G×E studies may contribute to our understanding of resilience mechanisms. For this, we focus on common variants in three candidate genes that may moderate the effect of adverse life events on psychiatric disorders and related intermediate phenotypes: the corticotropin-releasing hormone receptor 1 gene (*CRHR1*), the FK506 binding protein 5 gene (*FKBP5*), and the serotonin transporter gene (*SLC6A4*). These three genes were selected based on the wealth of studies across a range of different phenotype levels and the presence of functional studies as well as for the purpose of illustrating the concept of convergence across levels of investigation. They are not meant to be exhaustive of the literature on G×E in the context of risk and resilience, which has recently been reviewed (3,4). *CRHR1* is a G protein–coupled receptor that binds corticotropin-releasing hormone, a peptide that plays a key role in activating signal transduction pathways involved in the stress response (7,8). *FKBP5* encodes a co-chaperone of heat shock protein 90 that moderates stress hormone/glucocorticoid receptor (GR) function (9). *SLC6A4* encodes the serotonin transporter, the target of selective serotonin reuptake inhibitors. For *SLC6A4,* the most commonly studied polymorphism is a repeat polymorphism (the short allele and long allele) in the promoter region (5-HTTLPR polymorphism) [for details, see (10)].

The literature examining G×E effects for *CRHR1, FKBP5,* and HTTLPR has recently been comprehensively reviewed in a number of articles (3,4,8,9). The aim of this conceptional review was to illustrate convergence of findings across these

exemplary genes and to illustrate how G×E studies might inform our understanding of resilience mechanisms. A first observation in this regard is that the common variants in all three genes have risk-modifying properties that are not confined to a single psychiatric diagnosis but rather go across diagnostic categories (4). This is in line with the conceptualization of resilience as an active process that aids the maintenance of homeostasis within a broad range of environmental circumstances (1) as opposed to resilience constituting merely the lack of disease-specific risk factors. In fact, the same polymorphisms in these three genes have been shown to moderate the effects of adversity on the development of major depressive disorder (MDD) (9,11–17), posttraumatic stress disorder (18–27), and alcohol use disorder (28–32) as well as other psychiatric disorders, including first-onset psychosis (33,34). This suggests that genetic variation in these genes may influence disease risk by moderating proximal shared resilience mechanisms. This raises the question as to which common physiological processes are modified by these gene variants.

Part of the answer might come from studies that investigated the same G×E effects on measures of intermediate physiological, cognitive, or neural processes that likely underlie risk for psychiatric pathology across specific phenotypic expressions (35). The next section summarizes evidence of convergence of risk-moderating gene variants onto the same intermediate phenotypes, focusing on the stress hormone response as one example, which by all means is not meant to be an exhaustive representation of intermediate phenotypes relevant to resilience.

Convergence Onto Intermediate Phenotypes

Regulation of the stress hormone system within the hypothalamic-pituitary-adrenal (HPA) axis is central in adversity-related disease risk, with both blunted and exaggerated responses reported following exposure to stressful life events and in disease states (36,37). The set point of this system has been studied with psychological and pharmacological challenge tests (38,39) as well as physiological endocrine measurements (40). All three genes' polymorphisms have been shown to alter these measures, with the so-called risk alleles often associated with an exaggerated or prolonged response of the system (41–59). For *FKBP5,* these findings extend to prolonged endocrine responses to psychosocial stressors (41,47,50), altered responses to pharmacological challenges (53), and physiological HPA axis measures (48,49). Similarly, *CRHR1* risk haplotypes have been shown to modulate responsiveness to psychological challenge tests (51,56), pharmacological challenges (46,58), and diurnal cortisol regulation (57). The 5-HTTLPR polymorphism has been most extensively studied in this regard, with meta-analytical evidence for a heightened endocrine response to psychosocial stress among carriers of the risk/short allele (54), with evidence for a stress response modulatory role across species already during infancy (42–44,52,55). These results support the notion that disease risk-modifying properties of these gene variants may in part be mediated through regulatory effects on HPA axis set points. The polymorphisms may affect different parts of the stress response, from activation to negative feedback, and depending on context, risk alleles may be associated with different HPA axis outcomes and yet overall promote homeostasis. These findings suggest that different genetic variants might contribute to resilience by moderating the effects of the environment on the same physiological mechanism.

It is worth noting that convergence is evident not just for HPA axis functioning but also for other intermediate phenotypes that are associated with risk and resilience across mental disorders such as neurocircuit measures of threat responsiveness (60–68) and neuroticism as a personality trait (69–74) (Figure 1).

While the presented candidate G×E studies may provide a roadmap for investigating mechanisms of resilience, it is clear that they are likely underpowered, with inconsistent results reported [e.g., in the interaction between the 5-HTTLPR and early life adversity on depression risk (15,71,75–77)] and no support in large cohort studies (6). Similarly, there are also negative findings regarding the moderating effects of the *FKBP5* haplotype on anxiety and depression (17,78,79) and inconsistent findings for *CRHR1* (14,80). Inconsistent findings also exist regarding the discussed findings in intermediate phenotypes, with only few findings having been confirmed in large meta-analyses (54,66,67,71). There are many potential sources for such inconsistencies, the most important being differences in the assessment of environmental risk, with timing, type, and duration likely affecting these interactions and differences between self-reported and objective measures of adversity (5,81–83). Additive and interactive effects of different environments have been reported but are often not considered, and genetic effects have been shown to be diminished (27), but also unmasked (21), with increasing levels of adversity. Other potential sources are heterogeneity of phenotype definition and assessment (84,85) but also insufficiently powered studies. In addition, individual single nucleotide polymorphisms (SNPs) contribute only a very small proportion of the overall variance.

Genome-wide Strategies

Genome-wide G×E studies (GEWISs) represent a powerful unbiased approach for the identification of gene variants that modify environmental risk and hence can inform about the genetic basis of resilience mechanism. This has proven to be successful in other areas of medicine (86–88). To date, only a few GEWISs have been conducted in psychiatry, the majority of which examined the effect of stressful life events on depression phenotypes (89–93). The largest GEWIS in psychiatry to date investigated the interaction of adult stressful life events with common gene variants on depression symptoms in a UK Biobank sample (~100,000 subjects) and a Generation Scotland sample (~5000 subjects). The study yielded inconsistent evidence for the presence of gene × adult stressful life events on depressive symptoms (89). GEWISs have two main limitations. First, there is limited power to detect the small effect sizes of each individual G×E inherent to the polygenic nature of complex disorders. Second, even more so than in candidate G×E studies, large sample sizes often come at the cost of detailed and in-depth phenotyping. This likely contributes to the inconsistencies in GEWISs.

To circumvent power issues, the use of polygenic scores (PGSs) has become increasingly popular, with the aim of

capturing a larger amount of the trait-associated genetic variance with a single measure. PGSs are in principle weighted additive scores of all alleles that are associated with a trait of interest in a genome-wide association study (GWAS) (94). Such PGSs, based on large GWAS meta-analyses, have been shown to explain a substantial proportion of variance in psychiatric phenotypes, such as schizophrenia (95), and have also been used to explore G×Es. The largest PGS×E study to date applied an MDD PGS from a subsample of the Psychiatric Genomics Consortium wave 2 MDD GWAS cohort to a sample of 5765 subjects, with childhood trauma as the environmental parameter (96). This study showed evidence for additive, but not interactive, effects of this PGS and childhood trauma on MDD. Overall, this study and previous conflicting findings of MDD PGS×E effects on depression (96,97) and a recent study investigating the MDD PGS in children (98) do not support a consistent interaction of this PGS with early adversity.

In addition to its contingency on a sufficiently high-powered GWAS, the PGS×E approach suffers a more inherent conceptual limitation that might contribute to the inconsistent findings. The PGSs in all studies to date are weighted by a main effect on disease risk and not an interaction effect. However, it is possible that common genetic variants showing interaction effects might not have strong main effects on the target trait (99). Here alternative strategies could be of interest.

BOTTOM-UP MAPPING OF G×E: FROM MOLECULES TO INTERMEDIATE PHENOTYPES TO DIAGNOSES

Another avenue toward the identification of resilience mechanisms and intermediate phenotypes could follow a bottom-up approach that starts with mapping regulatory gene variants associated with heightened sensitivity to environmental stimuli on a molecular level.

Exposure to environmental stimuli leads to a cascade of effects that, in the case of adversity, culminates in the activation of stress response systems such as the catecholaminergic system and the stress hormone system. This leads not only to a number of physiological changes but also to induction of changes in gene transcription and likely also epigenetic changes, especially with the activation of the GR. Several studies have indeed shown that GR activation leads to cell-specific transcriptional changes in thousands of genes as well as local epigenetic changes (100,101). A reduction of DNA methylation has been reported for some loci, which makes the transcript more responsive to subsequent GR stimuli (102). Possible mechanisms of resilience could directly relate to genetic moderation of these very proximal responses to stress, that is, greater or lesser impact of the environmental stimulus on the transcriptional or epigenetic level.

FKBP5: From Moderation of the Transcriptional Response to Disease Risk

FKBP5 was initially reported as a gene that is strongly responsive to glucocorticoids and in turn affects the regulation of the stress hormone system by altering GR sensitivity via direct protein–protein interactions (103) In a study examining genetic variants associated with antidepressant treatment response, we had initially identified that a haplotype in *FKBP5* that moderates the induction of *FKBP5* messenger RNA by GR activation (104) and hypothesized that such a differential induction at the molecular level could also moderate long-term risk to psychiatric disorders after exposure to early adversity (18). In fact, a number of studies have now reported an interaction of this haplotype with early adversity to predict a range of psychiatric symptoms, as described in the first part of this review. The most likely functional SNP within this haplotype, rs1360780, alters a TATA box binding site close to a glucocorticoid response element in intron 2 of the gene. The allele with high messenger RNA induction that is also the risk allele leads to the presence of such a binding site and an altered three-dimensional conformation, with the glucocorticoid response element in intron 2 coming in proximity to the transcription start site (21). This genetic variant seems to alter direct effects of glucocorticoids not only on *FKBP5* messenger RNA but also on DNA methylation levels in regulatory elements of this gene. In fact, only individuals exposed to early adversity and carrying the high-risk haplotype also show reduced DNA methylation at another intronic glucocorticoid response element. In reporter gene assays, this reduction in DNA methylation led to increased responsivity of the target gene to glucocorticoids and correlated with GR sensitivity (21). This supports a model in which functional genetic variants and exposure to early adversity lead to prolonged GR activation via increased FKBP5 levels, which in turn has been shown to induce local DNA demethylation at the site of receptor binding (9). This reduced DNA methylation in an enhancer region increases the response to subsequent exposure to glucocorticoids, so that in exposed individuals carrying the risk haplotype both genetic and epigenetic factors lead to a disinhibited FKBP5 response. Only these combined effects seem to increase disease risk given that main effects of the *FKBP5* genotypes are not consistently reported. FKBP5 levels may reach only a certain threshold following this dual disinhibition, leading to altered downstream pathways of glycogen synthase kinase 3β or calcineurin signaling (105), decreased spine density (106), and behavioral effects such as increased anxiety and decreased stress coping (107,108).

Mapping Molecular G×E on a Genome-wide Level

Investigating genetic variants that moderate the impact of environmental exposures on molecular response on a genome-wide level could thus identify novel genetic variants moderating risk and resilience to disorders. Such approaches have been proposed in general for the study of complex disease (109), and examples have been described in toxicology (110). Argos *et al.*, for example, explored the impact of genome-wide SNP × arsenic exposure on arsenic-associated gene expression and DNA methylation in peripheral blood to preselect SNPs that would moderate the extent of skin lesions with exposure (110).

We have adapted such screening approaches to follow up on our finding relating to FKBP5 that variants that moderate the transcriptional impact of glucocorticoids could be of interest for stress-related psychiatric disorders. For this, we have mapped common regulatory gene variants associated with a differential transcriptional response to the GR agonist

dexamethasone (111), mimicking the activation of this receptor following stress exposure. These genetic variants are located in long-range enhancers with brain and cross-tissue relevance and are significantly more likely to show associations with MDD or schizophrenia in large GWASs than variants moderating baseline gene transcription (111). This suggests that an altered molecular responsivity to glucocorticoids contributes to risk for MDD and schizophrenia, with both disorders showing increased prevalence following exposure to early adversity. By constructing a PGS from the functional GR response SNPs that also associate with MDD, we found that this score that reflects a different molecular sensitivity to stress is also associated with an inappropriate amygdala activation during emotional fear processing (111) and increased cortisol secretion in response to a psychosocial stressor (112). In addition, this PGS also significantly correlated with both baseline values and stress-related changes of the brain's hemodynamic response function (HRF) (112). These HRF changes also correlated with a regulatory gene variant of *KCNJ2,* a gene that mediates glucocorticoid effects on neurovascular coupling in rodents (113). This supports the notion that the observed HRF changes reflect stress-related changes in neurovascular coupling, rendering HRF changes a promising novel intermediate stress phenotype that could help to link the action of stress effectors to pathological findings of chronic stress such as structural changes in the limbic system or prefrontal cortex (114).

In addition to gene expression, epigenetic changes, including DNA methylation, present another interesting intermediate phenotype for such approaches. Environmental perturbations can alter the epigenome, leading to sustained changes in gene transcription and thereby providing a molecular mechanism for altered biological processes following adverse environmental exposures and ultimately altered psychiatric risk later in life (115–119). Epigenetic changes are influenced by not only environmental factors but also genetic variation (21,120), so that epigenetic mechanisms could represent a molecular point of convergence for G×Es. Studies focusing on the developmental impact of adverse environment on the epigenome have shown that the environment alone is rarely the strongest predictor of epigenetic differences. Rather, environmental and genetic factors likely have additive or multiplicative roles in shaping the epigenome and consequently modulate phenotype presentation and disease risk (121). Teh *et al.* investigated the contribution of the prenatal environment as well as genetic variation in *cis* on DNA methylation of umbilical cord tissue in 237 neonates (122). The authors concluded that the large majority of interindividual DNA methylation variability was best explained by the interaction of genotype with different in utero environments rather than the environment or genetic variant independently. More recently, Czamara *et al.* extended these findings by exploring the influence of the prenatal environment and genotype on variably methylated regions in more than 2000 newborns (123). Their study confirmed that interactive and additive effects of genetic variation and prenatal environment were the best predictors of DNA methylation patterns as compared with genetic or environmental predictors alone. Importantly, their study could also show that genetic variants interacting with prenatal environment were enriched for disease-associated variants from large GWASs, including psychiatric disorders (123). While methylation quantitative trait loci have been previously used to functionally annotate GWAS findings, variants with G×E effects on DNA methylation extend these annotations because they often do not have a strong main genetic effect.

Genetic variants may influence outcome following exposure to adversity by either directly or indirectly altering the molecular consequences of exposure. Transcription factor–mediated epigenetic changes, such as the ones reported for the GR, could represent a possible target mechanism. Genetic variants may directly alter the binding affinity of the factor to the target enhancer site or may indirectly alter the activation of the factor and thus its downstream epigenetic consequences. Both the differential susceptibility hypothesis and diathesis stress hypothesis could be supported at this level with a number of possible different combinatorial mechanisms that are illustrated in Figure 2.

FUTURE DIRECTIONS

Studying G×Es may provide a tool to dissect mechanisms of resilience. Studies exploring G×E on diagnostic outcomes have had a major conceptual impact on the field (13,81) but are fraught with issues of lack of replication. This relates to power issues, with initial discoveries in small samples, but also inherent problems of our field, with symptom-based and not mechanism-based diagnoses, increasing the heterogeneity within current diagnostic groups. In addition, current studies rarely rely on objective measures of environmental factors, and especially retrospective reports of adversity show only poor agreement with prospective assessments (124). In addition, most studies focus on one or a few environmental factors; however, it is clear that environmental factors influence each other and combine both positive and negative factors. To better address these complex interactions, the concept of an exposome has been brought forward in the study of complex disease (125). In fact, the National Institutes of Health–initiated Environmental influences on Child Health Outcomes program (which includes neurodevelopmental outcomes) has adopted a strategy of integrated exposure analysis, including inorganic and organic toxicants, nutrients, and social stress markers (126). Recent technological developments will facilitate more objective measures of environmental factors by integrating geographic information systems, remote sensing, and geolocation technologies but also portable and personal sensing that include smartphone-based sensors and assessments (127). Especially the latter will allow more reliable assessments of stressful life events. Large longitudinal cohorts, optimally starting at preconception and including such repeated measures, will be necessary for exposome × gene interaction analyses.

Technological advances will also improve our capacities for bottom-up mapping. For now, these approaches have mainly used molecular data derived from peripheral tissues, including blood. While peripheral blood is an important surrogate tissue, with immune cells likely contributing to the risk for a number of psychiatric disorders (128), it would be important to also investigate living cells from the peripheral nervous system at different developmental stages. This is now possible with the

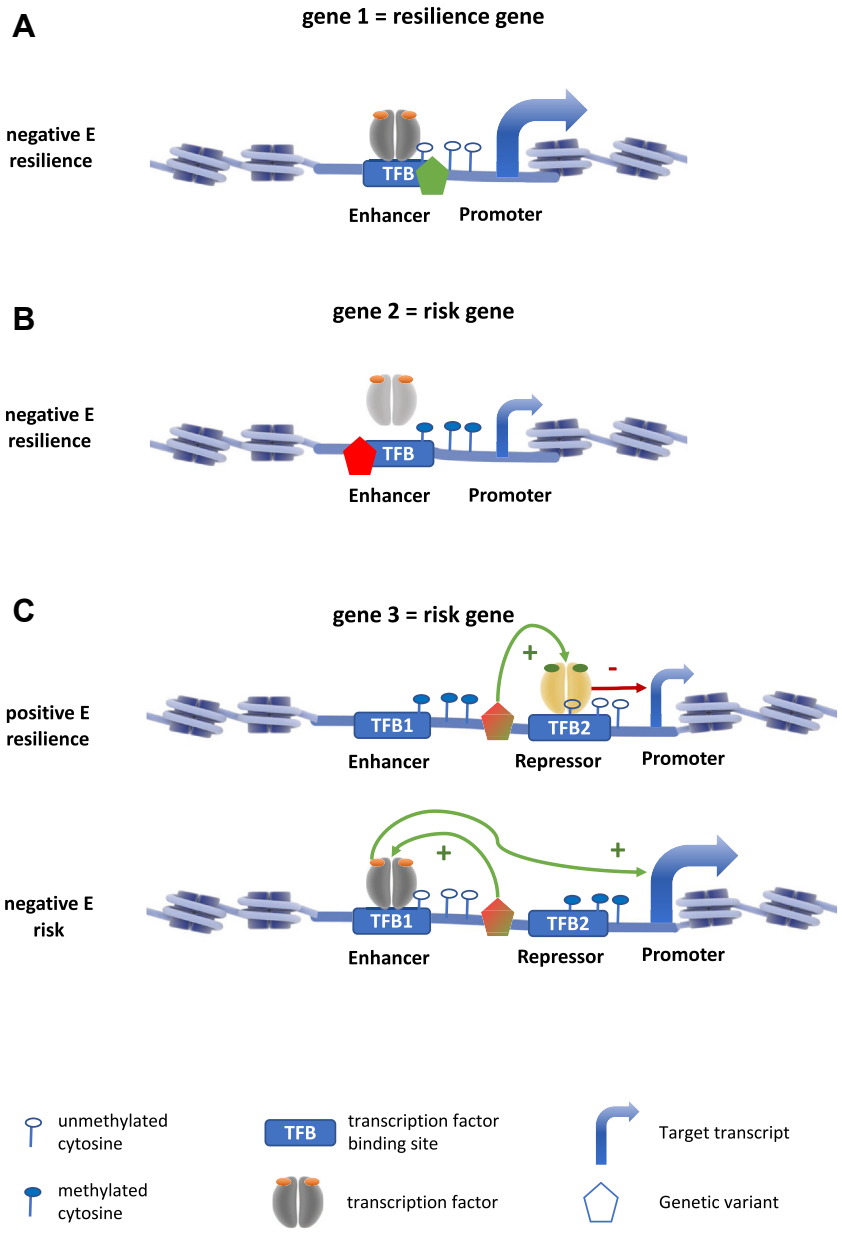

Figure 2. Illustration of how genetic variants may promote risk or resilience via affecting epigenetic regulation in gene regulatory elements. **(A)** Situation in which a genetic variant is associated with epigenetic changes (reduction in DNA methylation) that increase binding of a transcription factor that would enhance the transcription of a gene that promotes resilience mechanisms. **(B)** Situation in which a genetic variant is associated with epigenetic changes (increase in DNA methylation) that decrease binding of a transcription factor that would enhance the transcription of a gene that promotes risk mechanisms. Overall, in both scenarios, these variants would promote a decrease in disease risk in the light of adversity. **(C)** Scenario of a genetic variant that is associated with differential susceptibility. In conjunction with a positive environment, the variant is associated with epigenetic silencing of an enhancer of a risk gene and epigenetic activation of a repressor for the same risk gene, thereby decreasing the expression of that risk gene and promoting positive outcomes. The bottom part of **(C)** depicts the situation with exposure to a negative environment. Here, the genetic variant promotes epigenetic silencing of the repressor and activation of the enhancer, thereby overall increasing the expression of the risk gene and promoting risk. E, environment.

advent of induced pluripotent stem cell–derived systems and a number of robust methods to differentiate into progenitors and different neuronal subtypes but also glia cells (129) and derived self-organizing three-dimensional structures (130). Such systems would allow measuring the molecular response in cells of the nervous system to proxies of environmental stimuli in the context of common human genetic variation. While this approach is attractive, it currently has limitations. First, we still need to better understand the relevant downstream effectors of adversity. While glucocorticoids are one potential mediator, there are others that might not be that easily studied in vitro. Second, the generation and comparable differentiation of hundreds of induced pluripotent stem cells is currently still a labor-intensive and very costly endeavor. It is likely that a larger number of individual cell lines will be needed to reliably detect G×E on molecular features because, for example, gene expression profiles in induced pluripotent stem cell–derived motor neurons are more variable than those in primary neurons (131), thereby introducing additional noise. Large-scale perturbation assays, in which the functional effects of thousands of gene variants can be tested in a single cell line, may be an interesting avenue to overcome these issues and map G×E on molecular features (132,133).

Overall, exploring G×E to identify mechanisms of resilience could be a promising avenue, but a number of important challenges are still to be overcome.

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ARTICLE INFORMATION

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