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Review article

Genetic markers of the stress generation model: A systematic review

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ABSTRACT

Aim: Robust evidence suggests that depression, and risk for depression, are associated with the generation of stressful life events. This tendency to generate stress may be genetically determined. This systematic review aimed to identify specific molecular genetic markers associated with the generation of interpersonal stressful life events, at least in part dependent on individuals' behavior.

Method: We followed the PRISMA guidelines in searching six electronic databases (PubMed, MEDLINE, PsycINFO, CINAHL, Cochrane, and EMBASE) from inception to January 2021, and we reviewed the reference lists of eligible articles for additional records. We restricted eligibility to empirical studies involving at least one genetic marker and including proximal life events. We evaluated the risk of bias using the Newcastle Ottawa Scale for observational studies. The outcome permitted a distinction between life events dependent on the individual's agency versus independent events.

Results: Seven studies, including 3585 participants, met eligibility criteria. Three were longitudinal, and four were cross-sectional; six included adolescents and young adults, and one focused on middle adulthood. Four examined the serotonin-transporter-linked promoter region (5-HTTLPR), two examined the rs53576 single nucleotide polymorphism of the oxytocin receptor gene (OXTR), and one examined a multilocus genetic profile score including four hypothalamic-pituitary-adrenal (HPA) axis genes. There were no significant direct correlations between genotype and life events in any study. Instead, their relation was significantly moderated by symptoms, exposure to early adversity, or attachment. Consistent with the stress generation hypothesis, this moderation relation was significant in predicting exposure to *dependent* life events but was not significant in predicting *independent* life event exposure.

Conclusions: There is evidence that genetic variation in the serotonin, HPA axis, and oxytocin systems moderates the effects of psychosocial vulnerability markers on the generation of proximal, dependent life events. Future research should examine additional genetic markers in systems known to confer risk for stress generation.

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1. Background

Globally, depression affects nearly 300 million people and is the worldwide leading cause of morbidity (Herrman et al., 2019). Exposure to stressful life events (SLEs) is the strongest proximal trigger of depression onset. Careful prospective behavioral genetic research shows that the association between SLEs and depression is causal (Kendler et al., 1999). Exposure to life events is not random, however. A key driver of this vulnerability is the tendency of depression-vulnerable individuals to select themselves into high-risk environments (Kendler and

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Karkowski-Shuman, 1997a). This is an example of what Plomin et al. referred to as 'active genotype-environment correlation,' or the individual's tendency to contribute to their environment actively and even seek out environments consistent with their genotype (Plomin et al., 1977).

A special case of active genotype-environment correlation is "stress generation" (Hammen, 1991, 2020). The stress generation hypothesis of depression proposes that some individuals with a history of depression, or depressogenic vulnerabilities, may generate SLEs due, at least in part, to maladaptive personality characteristics that may be genetically mediated. One of the unique insights reflected in this hypothesis is that not all environmental contexts can be generated. In particular, the stress generation hypothesis distinguishes between SLEs that are dependent on an individual's characteristics or behaviors (e.g., the break-up of a romantic relationship, getting fired from a job due to incompetence) and those that are independent or 'fateful' (e.g., death of a relative by cancer) (Hammen, 1991). A very robust literature has provided support for the basic tenets of the stress generation hypothesis; specifically, individuals with depression report higher prospective rates of exposure to dependent, but not independent, life events than non-depressed groups (Liu, 2013; Hammen, 2020). The stress generation hypothesis has subsequently been extended to other clinical conditions, including bipolar disorder and borderline personality disorder (Allen et al., 2020; Alloy et al., 2020). Further, healthy individuals with particular risk markers for psychopathology, such as maternal history of depression, are also at greater risk for generating dependent stress than those without (Adrian and Hammen, 1993).

Stress generation is an important clinical phenomenon that has negative prognostic implications in depression. Longitudinal studies have confirmed that stress generation contributes strongly to the chronicity and recurrence of depression (Hammen et al., 2012) and is related to inadequate response to depression treatment (Bulmash et al., 2009; Fournier et al., 2009). Further, individuals at risk for stress generation have shown high continuity of stress exposure over decades (Hazel et al., 2008). This long-term stress burden imposed by stress generation has considerable maladaptive consequences for physical and mental health (McEwen and Morrison, 2013). Therefore, understanding the mechanisms underlying the generation of stress has implications for depression prevention (Hammen, 2020).

Using twin designs as a proxy for genetic risk, early behavioral genetics research set the stage for considering genetic background as a risk factor for stress generation. For example, using data from their sample of over 2000 female twin pairs from the Virginia Twin Registry, Kendler and colleagues found that lifetime history depression in the co-twin significantly predicted odds of exposure to dependent life events in the proband, including marital problems, divorce, job loss, and financial problems (Kendler et al., 1993; Kendler and Karkowski-Shuman, 1997b, 1999). Moreover, these associations held even after controlling for the proband's own current level of depression. In contrast, the twin's liability to depression did not predict odds of exposure to independent events in the proband, including deaths or illnesses of others, or being the victim of a robbery or other crime (Kendler et al., 1993, 1999). However, only very recently have studies begun to examine which particular set of *molecular* genetic markers drive associations with dependent versus independent SLEs.

For the past 20 years, molecular genetics research incorporating SLEs has focused on predicting depression as the outcome from an interaction of molecular genetic markers and distal (e.g., childhood maltreatment) or proximal (e.g., past-year SLEs) stress exposure. Early GxE work in depression focused specifically on a polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR). Several studies reported that individuals homozygous or heterozygous for the short (S) allele of the 5-HTTLPR—showing less transcriptional activity and lower serotonin uptake—had a greater risk for depression than those homozygous for the long (L) allele, but only in the context of stress exposure (Heils et al., 1996; Caspi et al., 2003). However, this work was subsequently criticized following several failures to replicate and the inability to detect robust effects through meta-analysis (Risch et al., 2009). Thus, while this research question has been revitalized somewhat by examining profile risk scores and using Genome-Wide Association Study (GWAS) designs, there is generally dampened enthusiasm for molecular genetics studies that predict depression outcomes in the face of stress due to a failure to replicate effects.

Far fewer molecular genetic studies exist examining SLE exposure itself as the outcome, and even fewer have examined the genetic markers involved in the generation of dependent SLEs, specifically. However, it is important to note that this latter design may be more powerful than the former for several reasons. First, depression is a very heterogeneous outcome with considerable variability in syndromal presentation, etiology, and pathology (Buch and Liston, 2021). In contrast, the generation of dependent life events may represent a more homogenous and transdiagnostic intermediate phenotype. Second, as noted above, the literature supports the basic stress generation phenomenon and supports proxies of genetic vulnerability (e.g., family history, twin designs) as a robust correlate. Finally, the generation of dependent stress is predicted by characteristics known to have a strong genetic basis (e.g., neuroticism) (Kushner et al., 2017).

Likely as a result of the large body of literature focusing on the 5-HTTLPR in molecular genetic work in depression, this marker has also received the most attention in the studies reviewed below examining stress generation as the outcome. Genetic markers in two additional neurobiological systems have also been targeted. First, variations in genes that regulate the function of corticotropin-releasing hormone (CRHR1 gene), glucocorticoid (FKBP5 gene), and mineralocorticoid (NR3C1 gene) receptors have all been associated with dysregulations in the cortisol response to laboratory stress and, thus, represent targets that may have implications for driving heightened exposure to stress (Derijk, 2009; Mahon et al., 2013; Zannas and Binder, 2014). Notably, the effects reported in these studies appear to be stronger in individuals with a history of childhood maltreatment, thus suggesting that the relation of these genetic markers to future stress processes may be moderated by distal stress exposure (Cicchetti et al., 2011; Sumner et al., 2014). Second, markers in the oxytocin system have been targeted due to the role of oxytocin in modulating attachment-related behaviors that may be relevant to the generation of interpersonal stress. In particular, the G-allele of the rs53576 SNP of the oxytocin receptor gene (OXTR) has been associated in previous research with various pro-social outcomes, including higher levels of empathy (Rodrigues et al., 2009) and pro-sociality (Kogan et al., 2011). In contrast, the A (minor) allele has been associated in these studies with negative social behaviors.

We provide the first systematic review of the molecular genetic correlates of stress generation. We expect the studies in this area to be heterogeneous regarding the diagnostic sample, genetic marker(s), design (cross-sectional; prospective), and stress assessment. Therefore, given the early state of this literature, we have chosen to conduct a broad, systematic review of all studies on this topic instead of limiting our focus to a homogenous subset of studies for meta-analysis. In addition, this review pays particular attention to evaluating the methodological rigor of stress assessment and its appropriateness for the stress generation hypothesis's specific predictions. Specifically, as mentioned above, a crucial distinction in addressing stress generation is between events that are dependent on, versus independent of, the individual's agency. Relatedly, it is critical for research in this area to assess the dependent variable (i.e., *exposure* to SLEs in the environment) with a measure that is not confounded by any biases inherent in the independent variable (e.g., genetically mediated personality traits) (Monroe and Reid, 2008; Karg et al., 2011). That is, the question posed in the current study, and the stress generation hypothesis in general, is not about whether individuals with particular genetic risk *perceive*, or appraise, their environments as more stressful; it is about whether these vulnerabilities are associated with heightened exposure to actual life events in the external environment. There is robust evidence that

contextual life event interviews that employ independent raters to assess the presence and severity of SLEs provide more valid and reliable measures of SLE exposure, unconfounded by subjective biases inherent in the correlate of interest (e.g., genetic risk, personality, state psychopathology) than self-report life event checklists.

Our overarching goal with this review is to summarize the state of knowledge on the molecular genetic markers of stress generation to stimulate further research bearing on this question. We hypothesize that, in general, risk makers in the 5-HTTLPR, OXTR, and HPA axis gene systems will be significantly associated with heightened exposure to dependent but not independent SLEs. Further, we hypothesize that these relations may be significantly moderated by distal stress markers, such as a history of childhood maltreatment.

2. Methods

2.1. Protocol and registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Liberati et al., 2009). In addition, we registered this review using PROSPERO (CRD42019136886).

2.2. Eligibility criteria

Eligible studies examined the relation of one or more genetic markers to the generation of proximal SLEs. We defined a genetic marker as any DNA sequence that causes disease or is associated with an illness (Wikipedia, 2021). We defined proximal SLEs as stressful life events occurring within 12 months of the life event assessment and assessed using a validated instrument. We included studies reporting the same sample so long as different biomarkers were considered. We excluded studies that did not contain proximal SLEs as a primary outcome. We also excluded studies that did not allow us to distinguish the types of proximal SLEs central to the stress generation hypothesis. Specifically, studies had to assess the relation of a genetic marker(s) to either (a) independent versus dependent life events separately or (b) clearly defined dependent events. To that end, the independent life events can be considered the control comparison. Therefore, we excluded studies that simply examined correlations between genetic marker(s) and an overall index of life events, collapsing distinctions based on event independence. As the primary outcome of interest in this review was the generation of proximal SLEs, we excluded gene-environment interaction studies with the presence or severity of psychopathology as the outcome (dependent) variable. Because the stress generation phenomenon has been documented across several clinical conditions and in healthy individuals at risk for psychopathology, we did not restrict study eligibility to particular clinical samples. We considered all study designs involving primary data collection (e.g., case-control, longitudinal prospective, randomized controlled trials). We excluded secondary studies, such as review articles, commentaries, letters to the editor, editorials, and post-hoc analyses of primary data sets. We also excluded studies without an English-language translation.

2.3. Search strategy

After meeting with an experienced research librarian, we developed a systematic review protocol involving six electronic databases. To identify pertinent studies, the following ten databases were systematically searched: AMED, ProQuest, Web of Science, PubMed, MEDLINE, PsycINFO, CINAHL, Cochrane, EMBASE, and two clinical trials registries. In addition, the following types of search terms were used: biomarkers, neurotransmitter transport proteins, plasma membrane neurotransmitter transport proteins, serotonin, dopamine, oxytocin, orexins, depression, and stress generation (**Appendix 1**). The initial searches were conducted in May 2019 from inception; however, a repeat search was done on January 21, 2021. We performed backward searches to complement this search (i.e., examining reference lists of eligible studies).

2.4. Selection of studies

Following the removal of duplicates, two co-authors (AB and EF) completed two independent rounds of screening (first by title and abstract and then by full-text review). Most discrepancies between reviewers were resolved by consensus after each screening; however, a third reviewer (KH) provided input on select articles' suitability.

2.5. Data collection process and items

Two co-authors (AB and EF) abstracted data from included studies and contacted study authors for data confirmation or clarification where necessary, and we resolved disagreements by consensus. We extracted the following data from each study: study author and title, aim, relevant background (as per the stress generation hypothesis), study design, a summary of the study population, investigated genetic marker, SLE assessment, a summary of findings, and study conclusion.

2.6. Risk of bias in individual studies

We extracted sufficient data to assess study quality using the Newcastle Ottawa Scale (NOS) for cohort studies (Luchini et al., 2017; Wells et al., 2019). The NOS uses a star system to evaluate nonrandomized studies regarding three domains of quality (selection, comparability, and outcome) using eight criteria: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, comparability of cohorts based on the design or analysis, assessment of outcome, sufficient length of follow-up for outcomes to occur, and adequacy of follow-up of the cohort. For each criterion, we assigned a star, with the sum of stars providing an overall quality score (maximum score: 8 points). Thus, studies with 6 points or higher were of the highest quality, studies that achieved a total rating of 3 or fewer points were of the lowest quality, and we rated those between 4 and 5 points as fair quality. We adapted this scoring system from a previous meta-analysis (Bahji et al., 2020b). Two co-authors (AB and EF) independently scored studies using the NOS and resolved discrepancies by consensus (**Table 2**). Note that we did not exclude studies based on their NOS rating.

2.7. Synthesis of findings

Given the small number of studies that emerged from our review and the very heterogeneous methods, we chose not to conduct a meta-analysis. Instead, we synthesized study findings using descriptive tables and thematic summaries, using previously described methods (Bahji and Stephenson, 2019; Elbatarny et al., 2019; Bahji et al., 2020a).

3. Results

3.1. Study selection

Seven studies (Starr et al., 2012, 2013; Thompson et al., 2014; Harkness et al., 2015; Brinksma et al., 2018; Ebbert et al., 2019; Huang and Starr, 2020) met the eligibility criteria for the systematic review (**Fig. 1**).

3.2. Characteristics of studies

We provide the characteristics of all studies in **Table 1**. Three studies included longitudinal designs (Brinksma et al., 2018; Starr et al., 2013, 2012) while the remaining four were cross-sectional (Thompson et al.,

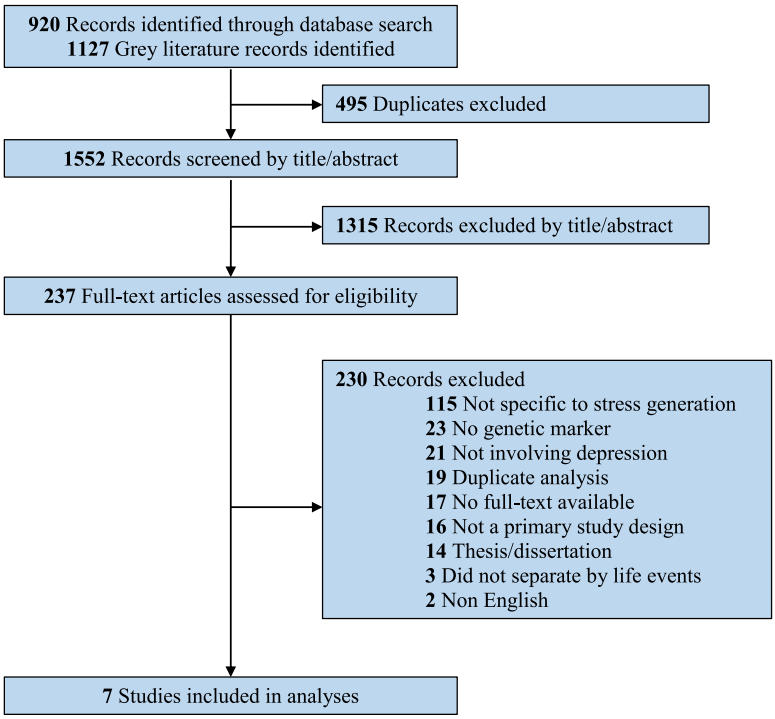

Fig. 1. PRISMA study flow diagram.

2014; Harkness et al., 2015; Ebbert et al., 2019; Huang and Starr, 2020). Across all seven studies, the total number of participants was 3585; however, the participants included in Starr et al. (2012, 2013) and Thompson et al. (2014) were drawn from the same larger sample and, thus, were overlapping. Six studies included adolescents and young adults, while one focused on middle adulthood (Ebbert et al., 2019). Four of the seven studies examined the serotonin-transporter-linked promoter region (5-HTTLPR) (Starr et al., 2012, 2013; Harkness et al., 2015; Brinksma et al., 2018), one examined an MGPS including 10 SNPs from four hypothalamic-pituitary-adrenal (HPA) axis genes (Huang and Starr, 2020), and two examined the rs53576 SNP of the OXTR (Thompson et al., 2014; Ebbert et al., 2019).

3.3. Direct tests of the stress generation hypothesis

Five studies had their explicit purpose of testing the stress generation hypothesis (Starr et al., 2012, 2013; Harkness et al., 2015; Brinksma et al., 2018; Huang and Starr, 2020). These five studies scored high on the Newcastle Ottawa risk assessment instrument, indicating high quality (**Table 2**). Four studies examined the 5-HTTLPR, and one examined the MGPS. All five studies included rigorous assessments of SLEs and analyzed the genetic marker's relation to dependent versus independent events separately. Specifically, four used gold-standard, contextual interviews of life events that employed independent judges to rate the severity and independence of events using standardized criteria (Starr et al., 2012, 2013; Harkness et al., 2015). One used a 22-item self-report checklist; however, endorsed SLEs were subsequently rated for independence by a team of judges according to the standardized criteria used in the contextual interview approach (Brinksma et al., 2018). None of these studies showed a significant direct correlation between the genetic marker and dependent or independent life events. Instead, in all five studies, the genetic marker's relation to life events was significantly moderated by a third variable. Consistent with the stress generation hypothesis, however, in all five studies, this moderation relation was significant in predicting exposure to *dependent* life events but was not significant in predicting exposure to *independent* life events.

Brinksma et al. evaluated a sample of 1306 adolescents from the Tracking Adolescent Individuals' Lives Survey (TRAILS) (Brinksma et al., 2018). They found that, among adolescents who were homozygous for the S-allele of the 5-HTTLPR, elevated symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) in middle adolescence significantly predicted the generation of dependent-interpersonal life events in late adolescence (β=0.20, p<0.001). However, ADHD symptoms did not indicate stress generation in those with the LS (β=0.03, p = 0.48) or LL genotypes (β=−0.04, p = 0.58). Further, neither genotype nor ADHD symptoms significantly predicted subsequent exposure to independent life events.

Similarly, in a sample of 381 adolescents recruited from the Mater University Study of Pregnancy who over-sampled for maternal depression, Starr et al. reported that among adolescents—who were homozygous or heterozygous for the S-allele of the 5-HTTLPR—elevated symptoms of depression at age 15 significantly predicted the generation of dependent-interpersonal life events at age 20 (β=0.24, p <0.001) (Starr et al., 2012). However, this association was not significant for those with the LL genotype (β<0.001, p = 0.99). Further, neither genotype nor depression symptoms significantly predicted exposure to independent life events at age 20.

Starr et al. subsequently analyzed data from 354 adolescents recruited from the same Mater University Study of Pregnancy (Starr et al., 2013). They found that, among adolescents who were homozygous or heterozygous for the S-allele of the 5-HTTLPR, lower levels of relational (attachment) security at age 15 predicted higher levels of dependent-interpersonal life events at age 20 (β=−0.15, p = 0.046). In direct contrast, among those with *high* relational security, the S-allele presence predicted significantly *lower* levels of dependent-interpersonal life events at age 20 (β=−0.20, p = 0.008). This latter result suggests that high attachment security served to buffer against adolescents' genetic vulnerability to generating interpersonal stress. But, again, consistent with the stress generation hypothesis, relational security did not predict stress generation in those with the LL genotype (β=0.13, p = 0.23). And, neither genotype nor relational security significantly predicted subsequent exposure to independent life events.

In a cross-sectional sample of 297 adolescents and young adults,

Table 1
Characteristics of included studies ($n = 7$).

Authors	Sample	Design	Assessments	Genetic Marker	Findings
Starr et al., 2012	Secondary analysis of 381 adolescents from the Mater University Study of Pregnancy. Adolescents were oversampled for maternal depression (60.9% female: 95% White)	Prospective longitudinal design: age 15 to age 20 waves	UCLA Life Stress Interview (Adrian and Hammen, 1993; Hammen and Brennan, 2001; Rao et al., 1999): Contextual life event interview employing independent judges to rate severity and independence of SLEs according to standardized criteria Beck Depression Inventory-II (Beck et al., 1996): 21-item self-report measure of presence and severity of depression symptoms	5-HTTLPR (SS, LS, LL)	Higher severity of depression symptoms at age 15 was significantly more strongly associated with higher levels of dependent-interpersonal SLEs at age 20 in adolescents homozygous or heterozygous for the S-allele of the 5-HTTLPR than in adolescents homozygous for the L-allele. There was no evidence for moderation in predicting levels of independent SLEs.
Starr et al., 2013	Secondary analysis of 354 adolescents from the Mater University Study of Pregnancy. Adolescents were oversampled for maternal depression (61.3% female: 100% White)	Prospective longitudinal design: age 15 to age 20 waves	UCLA Life Stress Interview (Adrian and Hammen, 1993; Hammen and Brennan, 2001; Rao et al., 1999) Bartholomew Relationship Questionnaire (Bartholomew and Horowitz, 1991): Self-report rating of attachment prototypes	5-HTTLPR (SS, LS, LL)	Among adolescents homozygous or heterozygous for the S-allele of the 5-HTTLPR, low relational security at age 15 predicted higher levels of dependent-interpersonal SLEs at age 20. Still, high relational security at age 15 predicted lower levels of dependent-interpersonal SLEs at age 20. There was no evidence for relational security to predict dependent-interpersonal SLEs among those homozygous for the L-allele of the 5-HTTLPR. Further, there was no evidence for moderation in predicting levels of independent SLEs at age 20.
Thompson et al., 2014	Secondary analysis of 441 adolescents from the Mater University Study of Pregnancy. Adolescents were over-sampled for maternal depression (59.2% female: 93.7% White)	Cross-sectional analysis at adolescent age 15	UCLA Life Stress Interview (Adrian and Hammen, 1993; Hammen and Brennan, 2001; Rao et al., 1999) Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First and Gibbon, 2004)" Structured interviews administered to mothers to assess the history of depression in the first five years of adolescents' life	OXTR rs53576 (AA, AG, GG)	Maternal history of depression significantly predicted higher levels of chronic interpersonal stress at youth age 15, but only for youth homozygous or heterozygous for the A-allele of OXTR.
Harkness et al., 2015	297 adolescents and young adults recruited from the community (77.6% female; 76% White; 50.5% in a current major depressive episode)	Cross-sectional	Life Events and Difficulties Schedule-II (LEDS-II) (Bifulco et al., 1989; Frank et al., 1997): Contextual life event interviews employ independent judges to rate the severity and independence of SLEs according to standardized and manualized criteria. Childhood Experience of Care and Abuse (CECA) interview (Bifulco et al., 1994): Contextual interview of emotional, physical, and sexual abuse employing independent judges to rate the severity of abuse according to standardized and manualized criteria.	5-HTTLPR (SS, LS, LL)	Participants homozygous or heterozygous for the S-allele of the 5-HTTLPR reported significantly higher dependent-interpersonal SLEs than those homozygous for the L-allele. However, this only occurred in those who had maternal emotional maltreatment or sexual maltreatment. There was no evidence for an interaction of childhood maltreatment and genotype in the association with levels of independent SLEs.
Brinksma et al., 2018	Secondary analysis of 1306 adolescents from the Tracking Adolescents' Individual Lives Survey (TRAILS; 50% female).	Prospective longitudinal design following adolescents across three time points, each two years apart. Adolescents ranged in age from 10.0 to 12.6 years at Time 1.	Long-Term Difficulties Questionnaire (LDQ) (Amone-P'Olak et al., 2009; Oldehinkel et al., 2015): Self-report questionnaire administered to child and parent to assess 22 SLEs. A team of independent judges subsequently rated SLEs as either "person-centered" (dependent-interpersonal) or "environment-related" (independent) ADHD Problems subscale of the Child Behavior Checklist (CBCL) (Achenbach, 1991): Parent report of 7 ADHD symptoms during previous six months	5-HTTLPR (SS, LS, LL)	Among adolescents homozygous or heterozygous for the S-allele of the 5-HTTLPR, higher severity of ADHD symptoms in middle adolescence (Time 2) predicted a higher number of dependent-interpersonal SLEs in late adolescence (Time 3). However, there was no evidence for this relation among adolescents homozygous for the L-allele of the 5-HTTLPR. Further,

(*continued on next page*)

Table 1 (*continued*)

Authors	Sample	Design	Assessments	Genetic Marker	Findings
					there was no evidence for moderation in predicting levels of independent SLEs.
Ebbert et al., 2019	614 participants in midlife (aged 40–65) recruited from the AS U Live Project (52% female; 71.6% White)	Cross-sectional	Childhood trauma questionnaire (CTQ) (Bernstein et al., 2003): Retrospective self-report scale assessing the history of emotional abuse Perceived social support and strain (Walen and Lachman, 2000): 12-item self-report scale assessing support and strain in the family, spouse/partner, and friend relationships	OXTR rs53576 (AA, AG, GG)	Among participants with higher levels of emotional abuse, those homozygous or heterozygous for the A-allele of OXTR reported significantly more strain in family relationships than those homozygous for the G-allele.
Huang and Starr, 2020	192 adolescents recruited from the community (53.1% female; 100% White)	Cross-sectional	UCLA Life Stress Interview (Adrian and Hammen, 1993; Hammen and Brennan, 2001; Rao et al., 1999) Youth Life Stress Interview (Rudolph et al., 2000): Contextual interview administered to parents to assess "interpersonal childhood adversity." An independent team of judges coded responses.	MGPS for 10 SNPs from four HPA axis genes: CRHR1 (rs4792887 T-allele, rs110402 G-allele, rs242941 T-allele, rs242939 G-allele, rs1876828 G-allele); NR3C1 (rs41423247 G-allele, rs10482605 T-allele, rs10052957 A-allele); NR3C2 (rs5522 G-allele); and FKB5 (rs1360780 T-allele)	Higher ICA was significantly associated with higher dependent-interpersonal stress among adolescents at high MGPS but not at low MGPS. However, this moderation effect was not significant for non-interpersonal or independent stress.

Note: ADHD = Attention Deficit/Hyperactivity Disorder; SLE=stressful life event; 5-HTTLPR: Serotonin-transporter-linked promoter region; MGPS = Multilocus Genetic Profile Score; SNP = Single Nucleotide Polymorphism; OXTR: Oxytocin Receptor.

Table 2
Newcastle Ottawa Scale of Study Quality for Cohort Studies.

Study	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcomes absent at the start of the study	Comparability of cohorts based on design	Assessment of outcome	Duration of follow-up	Adequacy of follow-up	Overall rating
Starr et al., 2012	*	*	*	*	*	*	*	*	High quality
Starr et al., 2013	*	*	*	*	*	*	*	*	High quality
Thompson et al., 2014		*		*	*				Low quality
Harkness et al., 2015	*	*	*	*	*	*			High quality
Brinksma et al., 2018	*	*	*	*	*	*	*	*	High quality
Ebbert et al., 2019		*		*	*				Low quality
Huang and Starr, 2020	*	*	*	*	*	*			High quality

Harkness et al. found that S-allele carriers of the 5-HTTLPR reported significantly higher dependent-interpersonal events than those in the previous three months homozygous for the L-allele (Harkness et al., 2015). However, this was only observed among those who reported a history of severe emotional maltreatment (β=0.22, p = 0.005). Furthermore, this relation of genotype to dependent-interpersonal events was not significant among those with no history of emotional maltreatment (β=0.02, p = 0.92). Further, neither genotype nor childhood maltreatment, or their interaction, were associated with reports of independent life events.

The final study included a cross-sectional sample of 192 adolescents (Huang and Starr, 2020). This study was the only in our review to go beyond a single genetic marker and used more sophisticated methods to calculate a local multilocus genetic profile score. Specifically, they created an MGPS using genotypes for 10 SNPs from four HPA axis genes: CRHR1 (rs4792887 T-allele, rs110402 G-allele, rs242941 T-allele, rs242939 G-allele, rs1876828 G-allele), NR3C1 (rs41423247 G-allele, rs10482605 T-allele, rs10052957 A-allele), NR3C2 (rs5522 G-allele), and FKB5 (rs1360780 T-allele). The authors used Pagliaccio's (2014) (Pagliaccio et al., 2014) established MGPS procedures. The decision to focus on HPA axis genes was based on meta-analytic literature confirming HPA axis dysregulation as a strong consequence of childhood adversity (Bernard et al., 2017). Consistent with the previous four studies' results, higher levels of childhood adversity are significantly associated with higher proximal dependent-interpersonal stress levels. However, this relation only emerged among adolescents at high MGPS (b=0.72, p<0.001) and not among those at low MGPS (b=0.03, p = 0.89). Further, this moderation effect was not significant for non-interpersonal or independent stress.

3.4. Indirect tests of the stress generation hypothesis

Two additional studies provided a preliminary test of the stress generation hypothesis (Ebbert et al., 2019; Thompson et al., 2014). Specifically, they examined dependent-interpersonal stress as an outcome but did not provide a contrasting examination of non-interpersonal or independent stress. Nevertheless, they are included in this review because they tested the hypothesis that genetic risk would predict stress exposure.

First, in a cross-sectional study of 441 15-year-old adolescents recruited from the same Mater University Study of Pregnancy as above (Starr et al., 2012, 2013), Thompson et al. found that those with a maternal history of depression reported higher levels of chronic interpersonal (i.e., relationship) stress than those without maternal depression (Thompson et al., 2014). However, this association only emerged as significant among participants who were A-allele carriers of the OXTR rs53576 SNP (interaction β=0.21, p<0.05). An essential strength of this study was that chronic interpersonal stress was assessed using a rigorous contextual interview with 'independent judges' ratings.

Second, in a cross-sectional study of 614 participants in middle adulthood (age 40–65), Ebert et al. examined the moderating effect of OXTR genotype on the relation of childhood emotional abuse on strain in adult relationships (Ebbert et al., 2019). They found a significant moderating effect in predicting strain in family relationships but no spouse/partner or friend relationships. Specifically, among those with a history of emotional abuse, those with the risk A-allele reported significantly lower self-reported quality of family relationships than those homozygous for the G-allele (statistics for the simple slopes were not reported). However, relationship strain was assessed in this study using a self-report questionnaire and was appropriately termed "*perceived* social strain." Therefore, the authors cannot rule out the interpretation that their effects are spurious, driven by the possibility that psychological factors under similar genetic control bias responses on the questionnaire. Further, as noted above, neither of the above two studies contrasted associations of the OXTR rs53576 to interpersonal stress with associations to non-interpersonal or independent stress.

4. Discussion

The purpose of the current systematic review was to critically review studies examining the molecular genetic markers associated with exposure to specific environments that are at least in part dependent upon or generated by the individual. Consistent with the stress generation hypothesis, all seven studies in the current review found evidence for a significant relation of genetic risk to exposure to dependent stressors, particularly in the interpersonal domain. In contrast, none of the five studies that included both dependent-interpersonal and independent stressors found a significant association of genetic risk to these latter stressors independent of the individual's agency. Importantly, in all seven studies, there was no evidence for a direct relation of genetic risk to dependent interpersonal stress; instead, this relation emerged only in the context of moderation by additional psychosocial vulnerabilities. These moderators included elevated levels of symptoms, and markers of a negative early environment, including a history of emotional maltreatment, interpersonal childhood adversity (e.g., death of, or separation from, a parent), maternal history of depression, and an insecure attachment style.

In general, the methods employed by these studies were robust. For example, all but one study used gold standard contextual methods for defining and rating stressful life events that minimize reporting bias. This is important because it strengthens conclusions that what is under at least partial genetic control is actual exposure to, or generation of, the stress in the environment, and not simply perceptions of, or sensitivity to, that stress. In sum, the seven studies included in this review provide consistent evidence that genetic risk, defined as the S-allele 5-HTTLPR, the A-allele of the OXTR, or multilocus risk in HPA axis genes, significantly raises the risk for the generation of acute and chronic proximal stress in individuals' interpersonal relationships in the context of additional psychosocial vulnerability.

Findings emerged most strongly for the 5-HTTLPR. All four studies investigating this marker differentiated relations to dependent-interpersonal versus independent stress with contextual stress assessment methods. Further, in two of these studies, the moderator variables were also assessed with rigorous independent interviews, and three studies included rigorous prospective designs. Several complementary mechanisms have been theorized to mediate the relation of the 5-HTTLPR polymorphism and stress generation, particularly in the context of elevated levels of symptoms and/or early psychosocial vulnerability. For example, the 5-HTTLPR polymorphism of the serotonin transporter gene has been theorized to mediate an amygdala-anterior cingulate-cortical circuit that underlies rumination (Pezawas et al., 2005). In addition, rumination is a common pathological feature of depression (Olatunji et al., 2013), a robust prospective predictor of dependent-interpersonal stress exposure (McLaughlin and Nolen-Hoeksema, 2012), and elevated among youth with a history of emotional maltreatment and/or maternal history of depression (Woody et al., 2016). In particular, Antypa and Van der Does report that young adults with a history of emotional maltreatment had higher levels of rumination than those without, but only among S-allele carriers of the 5-HTTLPR (Antypa et al., 2010). Therefore, perhaps youth with elevated symptoms or early vulnerability are only likely to generate stress in their interpersonal relationships if they are also at risk of ruminating on these vulnerabilities' causes and consequences.

The stress generation hypothesis also suggests that maladaptive personality characteristics and negative interpersonal behaviors drive the generation of conflict and tension in interpersonal relationships. Furthermore, there is evidence that the sorts of personality traits that underlie negative interpersonal behaviors, such as high levels of Neuroticism, are under genetic control by the 5-HTTLPR polymorphism of the serotonin transporter gene (Schinka et al., 2004). However, future research is needed to develop an integrated model for understanding how genetic risk and early psychosocial vulnerability are translated behaviorally into the generation of dependent interpersonal stress.

Similar results to the above were found in the one study examining an MGPS of HPA axis genes. Conclusions regarding the role of HPA axis genes in stress generation should be considered preliminary given the evidence space consists of just this one study. Nevertheless, the methods of this study were strong. First, it used rigorous contextual interviews of both proximal life event exposure and the moderator, childhood adversity. Second, instead of relying on a single genetic marker, it created an MGPS based on established procedures. The MGPS approach has been found to have greater predictive validity than examining single SNPs because the multiple SNPs are selected theoretically to capture the cumulative, polygenic effects of a specific biological system (Pagliaccio et al., 2014). The MGPS investigated by Huang and Starr has been shown to predict neuroendocrine, limbic, and affective reactivity to stress. Therefore, future research is required to determine whether these genetically linked mechanisms in the HPA axis system also drive the *generation* of stress in those with a strong history of early adversity.

Conclusions regarding the OXTR rs53576 should also be considered preliminary. First, neither of the two studies investigating this polymorphism contrasted the generation of dependent-interpersonal stress with independent stress. Further, these studies provided proxy measures for stress exposure and, in one, relying on subjective perceptions of interpersonal relationship strain. Therefore, the results of these studies should be replicated using more rigorous contextual interviews and rating measures. Nevertheless, these studies' findings suggest that negative early experiences predict later interpersonal stress more strongly in those at genetic risk for lower social competence. As noted above, the A-allele of the OXTR rs53576 has been associated with lower levels of trust, less accurate and empathic processing of social information, and less secure attachment. Therefore, it may be challenging for

A-allele carriers who grow up with a depressed mother or suffer emotional abuse to develop social competencies necessary for promoting healthy interpersonal functioning later in life. Future research is needed to identify the specific interpersonal processes affected by OXTR in the generation of stress.

4.1. Limitations and directions for future research

The current review is limited by the design features of the reviewed studies. First, one study did not employ a gold standard contextual interview. It thus cannot rule out depressive or other biases in driving the relationship of genetic risk to stress generation. Several authors have emphasized how important it is in genetic studies to use environmental measures that do not confound stress exposure with the stress response (Karg et al., 2011; Monroe and Reid, 2008). Second, all but one of the included studies focused on adolescent participants, and ethnic and socioeconomic diversity were limited. Third, it is important to note that three of the studies reviewed here included the same sample of participants, with minor variations in sample size based on inclusion criteria for each publication's specific analysis. Therefore, the results reported in this systematic review may be inflated, and more replication in independently collected samples is required. Finally, the psychosocial moderators across studies, including early adverse events, maternal depression, and attachment style, were diverse and suggested potentially unique mechanisms. Therefore, there is a need for future research to determine how each of these moderators uniquely relate to stress generation and, as such, whether they might prove differentially modifiable through intervention

The stress generation hypothesis offers exciting insights into the pathophysiology of depression. This review focused on genetics as one potential contribution to the stress generation hypothesis of depression, but this is a very open study area with many questions left to be explored. For example, future studies should expand to include additional genetic markers in neural systems associated with stress, such as Brain-Derived Neurotrophic Factor (BDNF) genes (Aso et al., 2008; Aguilera et al., 2009; Toyokawa et al., 2012). BDNF is critical for promoting neurogenesis, and decreased synthesis of BDNF in the context of risk polymorphisms of the BDNF gene have been associated with hippocampal atrophy and reduced telomere length following stress (Aguilera et al., 2009; Aso et al., 2008). The field also requires more studies using sophisticated genetic marker assessment, including creating MGPS or haplotypes or applying GWAS methods. These methodologies have been successfully employed in gene-by-environment interaction studies predicting psychopathology (Arnau-Soler et al., 2019; Feurer et al., 2017) and could be easily applied to gene-environment correlation (stress generation) designs. Also, there is solid and compelling evidence that early vulnerabilities, including a maternal history of depression and exposure to childhood abuse, induce epigenetic changes (Yehuda and Lehrner, 2018). These epigenetic changes have been shown to underlie, at least in part, the intergenerational transmission of depression (Sawyer et al., 2019). An intriguing hypothesis for future research is that interpersonal stress generation may mediate this relation. Finally, future research at neurobiological, cognitive-emotional, and behavioral levels of analysis is now required to elucidate the mechanisms that translate genotype into behavior to develop interventions that can remediate maladaptive interpersonal functioning among those at the highest risk.

5. Conclusions

The current systematic review is the first to integrate and critically evaluate the literature on the relation of molecular genetic markers to the generation of SLEs. Compared with the body of literature examining gene-by-environment *interaction* in predicting psychopathology, the gene-stress generation literature is in its infancy. Only seven studies were identified that examined the relation of genetic markers to SLEs relevant to stress generation (i.e., SLEs at least in part dependent on the individual's agency). All seven of these studies were consistent in finding no evidence for a direct relation of genotype to dependent SLEs. Instead, in all studies, the effect of genotype on stress generation was moderated by the additional vulnerability. However, consistent with the stress generation hypothesis, these moderation effects significantly predicted exposure to dependent- interpersonal stress but not independent stress. Therefore, these encouraging preliminary results support early behavioral genetics findings showing that exposure to the environment is partly under genetic control.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.114139.

Appendix 1. Search syntaxes

AMED (Allied and Complementary Medicine): 1985 to January 21, 2021		
#	**Searches**	**Results**
1	Stress generation.mp	5
2	Life events.mp	196
3	Depress*	7940
4	1 or 2	201
5	**3 and 4**	**54**

Cochrane Central Register of Controlled Trials: inception to January 21, 2021		
#	**Searches**	**Results**
1	Stress generation. mp	**0**
2	Life events. mp	4
3	Depress*	95,268
4	1 or 2	4
5	**4 and 5**	**1**

OVID Embase: 1947 to January 21, 2021		
#	**Searches**	**Results**
1	Stress generation. mp	604
2	Depress*	776,142
3	**1 and 2**	**116**
OVID MEDLINE (R): 1946 to January 21, 2021		
#	**Searches**	**Results**
1	Stress generation.mp	563
2	Depress*	510,734
3	**1 and 2**	**102**

OVID PsycINFO: 1806 to January 21, 2021		
#	**Searches**	**Results**
1	Stress generation. mp	236
2	Depress*	336,734
3	**1 and 2**	186

PubMed: inception to January 21, 2021		
#	**Searches**	**Results**
1	"Stress generation,"	547
2	Depress*	512,101
3	**1 and 2**	**102**

Web of Science Core Collection: inception to January 21, 2021		
#	**Searches**	**Results**
1	"Stress generation,"	1626
2	Depress*	579,397
3	**1 and 2**	288

CINAHL: inception to January 21, 2021		
#	**Searches**	**Results**
1	"Stress generation,"	326
2	Depress*	154,683
3	**1 and 2**	71

International Clinical Trials Registry Platform: inception to January 21, 2021		
#	**Searches**	**Results**
1	**"Stress generation," and depression**	**0**

ProQuest Dissertations and Theses Global: inception to January 21, 2021		
#	**Searches**	**Results**
1	"Stress generation" and "depression"	**1127**

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