

Review of the genetic basis of emotion dysregulation in children and adolescents

Drew Barzman, Chelsea Geise, Ping-I Lin

Drew Barzman, Chelsea Geise, Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229-3039, United States

Drew Barzman, Ping-I Lin, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH 45229-3039, United States

Ping-I Lin, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229-3039, United States

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Correspondence to: Ping-I Lin, MD, PhD, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, United States. pingi.lin@gmail.com

Telephone: +1-513-6363430

Fax: +1-513- 8037509

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Abstract

Previous evidence suggests that emotion dysregulation

may have different biological correlates between adults and children/adolescents. Although the role of genetic factors has been extensively studied in adult-onset emotion dysregulation, the genetic basis for pediatric-onset emotion dysregulation remains elusive. The current review article presents a summary of previous studies that have suggested a few genetic variants associated with pediatric emotion dysregulation. Among these candidate loci, many prior studies have been focused on serotonin transporter promoter gene polymorphism *5-HTTLPR*. Certain alleles of the *5-HTTLPR* gene polymorphism have been found to be associated with traits associated with emotion dysregulation, such as aggression, affect reactivity, and insecure attachment. Additionally, genetic variants involving dopamine and neurophysiological biomarkers like the *COMT* Val158Met (rs460) and dopamine receptor D2/ ankyrin repeat and kinase domain containing one polymorphisms may play a role in emotion dysregulation. Inconsistent findings have been noted, possibly due to the heterogeneity in study designs and characteristics of different populations. Further research on the role of genetic predetermination of emotion dysregulation in children and adolescents is warranted.

Key words: Gene; Emotion regulation; Adolescents; Children; *5-HTTLPR* polymorphism

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Core tip: Genetic correlates involved in emotion dysregulation in children and adolescents remain rather understudied compared to adult populations, despite the strong impact emotion dysregulation can have on an individual and societal functioning. This paper covers the key genetic variants involved in pediatric emotion dysregulation, with a special emphasis on the serotonin transporter promoter gene polymorphism *5-HTTLPR* typically associated with aggression, affect reactivity, and emotion dysregulation. This review places emphasis on

the necessity for further research in this field of study in order to better understand biological mechanisms underlying emotion dysregulation in children and adolescents, and also highlight current avenues of study worthy of further investigation.

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INTRODUCTION

Emotion dysregulation results from a failure to control, evaluate, and modify an emotional response to a stimulus, in particular the timing and severity of emotion, which often impacts externalizing behaviors^[1]. In children and adolescents, emotion dysregulation can be considered the outcome of the tendency to respond emotionally to a stimulus combined with the ability to most successfully modulate the response^[2]. These processes include conscious and subconscious mechanisms based in underlying genetic and neurophysiological entities. With the advances of high-throughput and high-resolution genomic technologies, research on the genetic basis of mood dysregulation has been increasing and empowering researchers to better understand how and why this dysregulation occurs in children and adolescents. Prior evidence has suggested that pediatric-onset form and adult-onset form of bipolar disorder, which is characterized by emotion dysregulation, may have distinct genetic predispositions and clinical outcomes^[3,4]. The purpose of this review is to summarize current genetics research findings within pediatric populations on emotion dysregulation and point out the need of more research to improved our understanding of genetic factors for pediatric emotional dysregulation. Unraveling age-dependent genetic mechanisms underlying emotion dysregulation will provide an initial step towards personalized medicines for mood disorders in children and adolescents. Although the body of research on genetic basis of pediatric-onset emotion dysregulation is limited compared to genetics research on emotion dysregulation in adults, several candidate genes have been consistently shown to be linked to emotion dysregulation in children and adolescents.

RESEARCH STUDY

A literature search with the key words related to genetic of emotion dysregulation in pediatric populations was conducted to gather information for this review article. Our query algorithm implemented in PubMed was as follows: required keywords were present in either "Abstract" or "Title" included (1) gene; (2) children

or adolescents; and (3) emotion or mood followed by regulation, reactivity, or arousal. Additionally, only human-based studies with English as the language were extracted. Certain parts of research from this review were selected and modified from a lecture written for Continuing Medical Education to Go for Physicians. A total of 19 studies were retrieved. Selected studies related to the genetics of pediatric emotion dysregulation are summarized in Table 1.

SEROTONIN TRANSPORTER GENE

5-HTTLPR POLYMORPHISM

The serotonin transporter gene (*5-HTT*) and a polymorphic serotonin-transporter-linked polymorphic region (*5-HTTLPR*) determine the quantity and duration of serotonin synaptic signaling during neurotransmission^[5]. There are three important variants of *5-HTTLPR* alleles: the short (S) allele, the long-rs25531(G) (La) allele, and the long-rs25531(A) (Lg) allele. The short (S) allele and the long-rs25531(G) (Lg) allele carriers^[6] compared to the long-rs25531(A) (La) allele variant carriers, have lower mRNA transcriptions of the serotonin transporter. Individuals without an La allele are found to produce approximately 50% less mRNA than individuals carrying homozygous La alleles^[7]. This polymorphism has been shown to correlate with the severity of affect reactivity and mood dysregulation^[8]. A meta-analysis of a serotonin transporter genotype and the activity of amygdala, a brain region modulating emotion regulation, reports that the *5-HTTLPR* polymorphism accounts for 10% of the variance of amygdala activation^[9]. Furthermore, the S allele has been shown to correlate with heightened amygdala activation in response to a broad range of emotional stimuli^[9,10]. In a study of 82 children and adolescents, individuals carrying either S or Lg allele were found to have more than two times the risk of aggressive behavior than individuals carrying at least one La allele^[5]. Borderline personality disorder, which is characterized by emotion instability, is also found to be associated with the short allele of the *5-HTTLPR* polymorphism^[11]. Another study on 91 adolescents reported that the effect of the short allele of *5-HTTLPR* on aggressive behaviors might be modified by attachment^[12]. These findings suggest that the *5-HTTLPR* polymorphism plays a role in emotion regulation, while environmental factors may also moderate its effect on mood symptoms and associated behaviors. More research is needed to validate these findings to have a better understanding of the role of this polymorphism in emotion regulation.

The *5-HTTLPR* polymorphism may also affect the cortical-limbic circuit critical for emotion regulation^[13]. Diffusion MRI examining the uncinate fasciculus, a white matter pathway that connects medial and orbitofrontal prefrontal cortexes to amygdala, in 37 female adolescents and adults and found the number of short alleles at *5-HTTLPR* inversely correlate with

Table 1 Summary of emotion dysregulation genetic correlates in children and adolescents

Genetic neural correlates	
5-HTTLPR low-expressing allele carriers Pacheco <i>et al</i> ^[13] Spangler <i>et al</i> ^[16] Gotlib <i>et al</i> ^[21]	Reduced white matter connectivity/ density in uncinata fasciculus Increased risk for development of disorganized attachment pattern Prolonged cortisol activity after a stressor
COMT Val156Met(rs460) Met Allele Carriers Boettinger <i>et al</i> ^[27] Waugh <i>et al</i> ^[24] Egan <i>et al</i> ^[25] Tunbridge <i>et al</i> ^[26]	Greater emotion dysregulation associated with dopaminergic systems
DRD2/ANKK1 Polymorphism Althaus <i>et al</i> ^[28]	5-HTTLPR S allele may predispose to (performance) anxiety, while DRD2 Taq1 A allele may predispose to the reward deficiency syndrome.

the fractional anisotropy (FA) values at white matter microarchitecture, especially in the left frontal region of the uncinata fasciculus. Uncinata fasciculus is a region believed to be the impetus behind the heightened amygdala reactivity and poorer functional coupling of amygdala and prefrontal cortex associated with emotion regulation abilities^[13]. In addition, age is positively correlated with FA values in the bilateral frontal regions of the uncinata fasciculus-which is consistent with data showing the increase in prefrontal activity and thereby emotion regulation due to myelination and development of prefrontal cortex during adolescence and adulthood^[13,14]. To date, there is no published evidence for the same phenomenon in males. Children carrying homozygous S alleles in the 5-HTTLPR polymorphism are also found to have greater activity of amygdala during visual processing of emotionally negative stimuli that mimics a transient depressed state than their peers carrying homozygous L alleles^[15].

Social and environmental adversity may also notably impact neuronal gene expressions (*i.e.*, epigenetic phenomena). Carriers of the S allele of 5-HTTLPR polymorphism have an increased risk for developing disorganized attachment patterns in comparison to homozygous L genotypes, while maternal responsiveness mediated the effect and acted as a type of safeguard against disordered attachment genetic predisposition^[16]. The study reveals that adolescents carrying the S allele show a greater emotional reactivity in response to restrictions of autonomy (defined as one's own goals as a method of self-regulation), compared with others carrying no S alleles^[12]. Another study found that childhood emotional abuse significantly moderated the relationship between genotype and the likelihood of quitting the behavioral indicator of resiliency to distress^[17], which is a validated game-like test designed to generate frustration and encourage the player to quit^[8]. Adolescents with one long (L) and one short (S) variant of the 5-HTTLPR polymorphism and poor family relations had a 12-14 time increased risk for high alcohol intoxication frequency^[18]. If family relations were poor, the SS genotype had higher alcohol consumption

than the LL genotype. The investigators suggest a possible heterosis, or increased functioning of the hybrid genotype, in cases in which the environment is unfavorable to adaptive functioning. The investigators did not, however, distinguish between high- and low-expressing L alleles, which may have contributed greatly to overall findings. Gerra *et al*^[19] found a significantly positive association of S-allele-carrier genotypes with irritability levels and related temperamental traits in adolescents. One large longitudinal study examined 4334 seven-year-old children and found no significant relationships between the 5-HTTLPR genotype and emotional symptoms in children, but those in the 5-HTTLPR low expression group demonstrated an increase in the risk for emotional symptoms when faced with minimal to moderate stress^[20]. These findings suggest that environmental effects need to be taken into account in elucidate the role of the 5-HTTLPR polymorphism in pediatric emotion dysregulation.

The S and the low-expressing L allele may also have a negative impact on stress reactivity and tolerance due to their positive correlations with prolonged cortisol secretion following a stressor^[21]. Even though the bulk of research on the 5-HTTLPR polymorphism and related factors in children and adolescents is considered preliminary, serotonin-related mechanisms have paved the way for novel treatment modalities relating to other biological systems that may have an impact on serotonin levels. For example, recent research on omega-3 fatty acids has been linked to a depletion in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) during early development, which may cause lower levels of serotonin and thereby incite a series of deleterious effects of mood dysregulation and stress reactivity, among other symptoms^[22]. While SSRIs have been used to treat mood dysregulation in children and adolescents for several years now, management of DHA and EPA levels is a novel therapeutic option. Learning more about mechanisms of serotonin regulation and manipulation within the brain can facilitate the development of more effective medication and treatment

plans.

OTHER GENETIC POLYMORPHISMS IMPLICATED IN EMOTION DYSREGULATION

While the bulk of pediatric research on genetic factors involved in emotion dysregulation focuses on serotonin, a number of other loci may also have an impact. A functional single-nucleotide polymorphism in the catechol-O-methyltransferase (*COMT*) gene encodes a valine to methionine mutation at position 158 (Val158Met) rs4680 in the enzyme that degrades dopamine^[23]. The Val variant has higher activity of catabolizing dopamine than the Met variant. Prior evidence has shown that the *COMT* Met allele is associated with more severe emotion dysregulation in children and adolescents^[24-26]. One study on 277 children and adolescents found that the Val allele carriers were more likely become irritable when their expected rewards are delayed, compared to their peers carrying no Val alleles^[27]. These results suggest that the role of *COMT* (Val158Met) polymorphisms in mood regulation may be complicated, as the relationship between dopaminergic tone and mood regulation may be non-linear.

The dopamine receptor D2 (*DRD2*)/ankyrin repeat and kinase domain containing one polymorphism are other genetic variants associated with D2 dopamine receptor binding affinity that may also play a role in emotion dysregulation^[28]. In a study of 65 children, the *DRD2* Taq A1 allele was found to be associated with a greater sensitivity and emotionality to negative feedback, while simultaneously diminishing one's sensitivity to positive feedback^[28]. The same study also found that children with the short allele (S) for the *5-HTTLPR* gene might show greater sensitivity to error processing in event-related potential experiments. Significantly enhanced early error-related negativity and later occurring error-related positivity were associated with the S-allele group compared to the homozygous L-allele group; such electrophysiological signals are thought to reflect the anterior cingulate activity^[28].

Other genetic variants associated with mood dysregulation have been reported by preclinical and clinical studies primarily focused on adults. The role of these variants in pediatric mood dysregulation also deserves some attention. For example, adult carriers of the monoamine oxidase-A (*MAOA*) promoter variant associated with a lower gene expression may have a higher propensity for aggression and impulsivity, compared with carriers of the *MAOA* promoter variant associated with a higher gene expression^[29,30]. Individuals with low-expression *MAOA* variant may have reduced left middle frontal gyrus activation and left amygdala and posterior thalamic activation in response to an anger trigger, compared to the control^[31].

Another genetic variant that may be of importance involves the cAMP response element-binding protein (*CREB*)-regulated transcription coactivator 1 (*CRTC1*), a *CREB* protein coactivator of the brain-derived neurotrophic factor (*BDNF*) implicated in rodent models of depression^[32]. One fMRI study of children found that a single nucleotide polymorphism (T/C) near the *CREB* gene might be associated with neural correlate for emotion reactivity-greater activation in the TT group, compared to the CC group, in the right dorsal anterior cingulate cortex, right putamen, right caudate nucleus and left anterior temporal pole, when the brain activity under a transient state of sadness^[33]. Mice lacking the coactivator have a series of negative traits, including impulsive aggressiveness, social withdrawal, and increased emotional response to stressful events^[34]. Mice without the *CRTC1* gene also demonstrate a reduced efficiency in serotonin and dopamine cycling in prefrontal cortex, as well as a decreased expression of susceptibility genes involved with neuroplasticity, including *BDNF*, providing a strong suggestion that the coactivator might play an important role in gene expression related to mood disorders. The L-type voltage-dependent calcium channel, alpha 1C subunit (*CACNA1C*) gene^[35,36] is linked to mood disorders from different populations. The calcium channel may also be linked to the arousal system^[37,38]. The calcium influx in the arousal system is modulated by glutamate^[39] and γ -aminobutyric acid (*GABA*)^[40]. The relationship between glutamate metabolism genes and mood disorders may be difficult to determine partly because such genes may be expressed in different brain regions. Research in these areas is essential to further understanding of psychiatric symptom etiology in children and adolescents.

DISCUSSION

There has been significant emerging evidence for the contribution of genetic variants to pediatric emotion dysregulation, thanks to the advances of genomic technologies. However, most of these genetic findings are challenged with the failure of replication across different populations, and hence genetic determinants of emotion dysregulation remain elusive. Inconsistent findings might continue to be a norm rather than an exception without taking into consideration the factors, such as genetic heterogeneity, clinical heterogeneity, and epigenetic phenomena associated with environmental influences. Current knowledge of genetic mechanisms underlying emotion regulation has been primarily based on research on adults, and hence more efforts to study the genetic basis for emotion regulation in children and adolescents are warranted. Some genetic variants (*e.g.*, *COMT* polymorphisms) have been found to exert paradoxical effects on emotion dysregulation in children, which may be partly attributable to a non-linear relationship between variants and neurochemical

changes and environmental influences (e.g., attachment). Additionally, the developing brain in the youth may further complicate genomic studies, as phenotypic features may fluctuate by age. For example, age-dependent changes in neural substrates related to empathy have been observed in individuals with autism spectrum disorders or typically-developing individuals^[41]. Additionally, autonomic arousal was uniquely heightened in adolescents^[42]. Furthermore, activities of prefrontal regions in response to emotions are also age-dependent^[43]. Finally, there are various psychological tasks related to emotion regulation associated with different brain circuits, and hence literature searches may be limited due to the heterogeneous contexts and terminologies. Nevertheless, the genetic component of emotion dysregulation constitutes an initial step of understanding the etiology of emotion dysregulation, but knowledge of hereditary and hormonal influences may yield robust improvements in pharmacological and therapeutic treatments that can benefit children and adolescents in managing dysfunctional emotional behaviors.

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