

Review article

Genetics of Adolescent Suicide: A Literature review

Anju Mathew, Naresh Nebhinani, Saboora Begum, Vijayakumar K, Moinak Banerjee

Address for correspondence: Dr. Anju Mathew, Department of Psychiatry, Government Medical College, Thiruvananthapuram, Kerala, India. Email: anjumathew2222@gmail.com

Abstract

Adolescent suicidal behavior is a global public health issue; however, genetic studies are sparse and diverse. A review of the current knowledge on the genetics of adolescent suicide based on an electronic search of two databases is being presented, following PRISMA guidelines. After identification, screening, and exclusion, 17 full-text articles based on original studies were included for the review. Studies indicate significant heritability for suicidal behavior. Aggression was found to be associated with higher rates of suicide attempts within families. Possible genetic variants, environmental changes, their interaction, and the timing of these interactions appear to be critical in deciding the suicidal behavior. Several candidate genes and pathways have been implicated with a focus on neurotransmitters, neurotrophic processes, stress response system, and the immune system. From the results, the serotonergic system seems to be the most plausible system explaining anxiety, impulsivity, depressed mood, and adolescent suicidal behavior. However, inconsistencies for serotonergic genes were also reported for adolescent suicidal behavior which largely reflected the ethnic and phenotypic variation. The serotonin transporter variant was significantly associated with depression and suicide attempts while serotonin receptor gene variants were significantly associated with suicide ideation. Tryptophan hydroxylase variant had a significant association with

suicide attempts, hopelessness, and impulsivity scores. Majority of the studies had a small sample size, and the lack of consensus on genetic studies reflected the phenotypic and ethnic variation. We need to develop a consortium for ethnic-specific observation by considering both genetic and epigenetic background and develop a consensus strategy to resolve phenotypic diversity for adolescent suicide.

Keywords: Genetic studies, association, phenotype, adolescent suicide, ethnic

Introduction

Suicide and self-harm among adolescents have been identified as a significant public health issue worldwide. Global data show that suicide is the second major cause of death among those aged 10 to 24 years [1-3]. More than 90% of the world's adolescent children live in low- and middle-income countries and they contribute to over 75% of global suicide deaths [1]. The tragic personal loss and the social and economic impact of these suicides are enormous on the family, friends, and society and demands urgent global attention.

Suicide is the fatal act of intentionally harming oneself. Suicidal behavior refers to a range of behaviors that include thinking (or ideation), planning, attempting suicide, and suicide itself. Etiological heterogeneity is often reflected by the significant differences in suicidal risk based on gender, age groups, geographic regions, and socio-political realities. Adolescent suicidal behavior is a complex human behavior, the cause of which consists of a constellation of interacting biochemical, genetic, psychological, and social factors [4,5]. Learning more about the precursors and risk factors of suicidal behavior is vital for preventing such high-risk behavior [6].

Clinical studies have shown that those who attempt suicide belong to a heterogeneous group depending on age, sex, intent, and lethality of attempt, impulsivity, past and family history, and

presence of psychiatric disorders [7]. This clinical heterogeneity may be due to an underlying genetic heterogeneity and hence, it is important to look into the genetic variables associated with suicide attempts in this population.

Genetic transmission may occur through specific genes and loci, and environmental transmission may occur through abuse or socio-cultural factors that impact the host epigenome [8-11]. Familial transmission of suicidal behavior has been explored in various studies. Twin and adoption studies suggest that the heritability of genetic factors can cause familial transmission of suicidal behavior to about 30-50% [12-15]. It has been shown that 11.3% of monozygotic twins and 1.8% of dizygotic twins were concordant for suicide [16]. Suicidal behaviors maybe transmitted as a trait within families, irrespective of psychiatric diagnosis [17]. Certain genetic association studies have been conducted, focusing both on candidate-gene and genome-wide (among adults), but the results were inconsistent and unsatisfactory [18]. It is suggestive of a polygenic risk model, with a large number of risk genetic variants aggregate towards contributing to risk [19]. The large heterogeneity within the groups of suicidal behavior compels for a call for a precise understanding of fallacies to resolve the conflicts of genetic studies and observations.

Among environmental factors, Early Life Adversity (ELA) such as parental neglect, physical, sexual or emotional abuse during childhood is found to increase the suicidal risk. Many studies have shown that ELA and lifetime suicide risk are interlinked [20-24]. Teen suicides are associated with different psychiatric disorders, including mood disorder, substance abuse, schizophrenia, conduct disorder, anxiety, and impulsive aggressive traits [25-27]. Various environmental stressors and psychiatric illnesses evoke changes within the biological systems of humans. Affected individuals usually display a hyperactive hypothalamic-pituitary-adrenal axis (HPA) and increased response to stress [28]. Reduced expression of glucocorticoid receptors in the

hippocampus due to epigenetic alterations induced by DNA methylation can impact the HPA axis [29]. Even the genes responsible for neuronal plasticity, neuronal growth, and neuroprotection are reported to undergo epigenetic modification [30,31]. These findings support the stress-diathesis model for suicidal behavior, which suggests that life stressors alone are not exclusively responsible for such behavior but this may aggravate an individual's genetic predisposition, which may trigger off the attempt [32,33]. Researchers have identified life stressors as both proximal and distal risk factors for suicide [34].

A large majority of the studies reflect the genetics of adult suicide but none specific for adolescents except for just one, that too almost a decade back [35]. Adolescent suicides are clinically different from adult and considering the enormous public health issue of adolescent suicide and varied knowledge of the underlying genetic risk factors, it was decided to look at the current understanding of the genetics of adolescent suicide. However, the scope of the present review is restricted to genetic observations in adolescent suicide.

Methods

Literature search

A literature search was conducted through the internet to update the knowledge on the genetic variations that lead to suicidal behavior among adolescents. An electronic systematic search of the databases, PubMed, and Google Scholar was done. All original studies on the genetics of adolescent suicide were included. The keywords for the search included “gene*”, “genome wide” “association”, or “polymorphism” in association with “adolescen*” and “suicid*”. The PubMed search term “*adolescen**” was used to get search results that included *adolescent* and *adolescence*. The term “*suicid**” yielded search results that included *suicidal ideation, suicide attempt, suicidal behavior, suicide completion, and suicidality*. Additional studies on the topic were identified from

the reference section of the selected articles and also from the citation list of these articles. Major literature reviews on adolescent suicide were searched to get any other relevant studies.

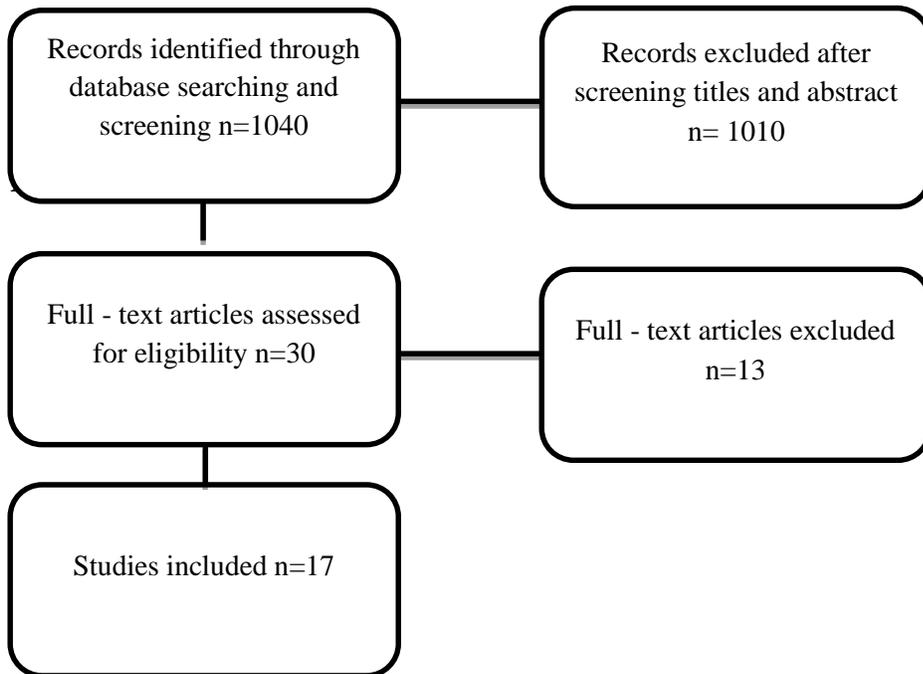
Study selection

Articles were included for the review if they satisfied the following inclusion criteria.

(1) Studies included human subjects (2) Study subjects belonged to adolescent age, 12 to 18 years (3) Paper was published in English (4) Studies analyzed the association between any genetic variation and adolescent suicidal behavior, including attempts and completion.

Duplicate papers and studies on non-human subjects were automatically excluded at this stage. The further exclusion was done after going through the title and abstract, to find out whether they fit into the inclusion criteria. The selected papers were clustered into two, “family-based studies” and “candidate-gene association studies”. We could not identify any “genome wide association studies” in this population and hence, this cluster which should have been there theoretically, was absent in this review. Because genetic studies on adolescent suicide are less, it was decided not to keep a time cut off and all available articles on the subject were selected. After screening the title and abstract and excluding the irrelevant ones, the relevant articles were selected for full-text review. Two reviewers did the study selection and data extraction independently. The discrepancies were corrected by a third reviewer, who made the final selection. The summary of the literature search strategy is shown in the flow chart (Figure 1).

Figure-1: Flow chart showing selection of genetic studies of adolescent suicide



A total of 17 full-text articles fulfilled the selection criteria on the genetics of adolescent suicide, including 7 family and 10 candidate gene association studies [17,36-51]. Five of these association studies followed a case-control design [39,43,46,48,51], and one had a combined family and case-control design [37]. Other studies were observational or comparative in design [41,42,45,47]. It was observed that the assessment parameters and sub-phenotype variability also extensively varied among study subjects.

The ethnicity of study participants was recorded which was largely Caucasian in origin. Clinical interviews using appropriate scales were performed in most of the studies which differed across studies. Blood samples were largely used while saliva samples were used in two studies [45,46] and cheek sample (buccal cell DNA) was analyzed in one study [42]. Most of the study participants belonged to the adolescent age group, 12 to 18 years of age. Some studies however included subjects up to 24 years and adult controls. A large majority of the participants were girls, though most of the studies had a nearly equal representation.

Family studies have concluded a familial transmission, independent of the presence of a psychiatric disorder [17] though later personality disorders were proposed to have a role [36]. Twin studies have looked into the familial aggregation of suicidal ideation, depression, and conduct disorder in adolescence due to shared genetic and environmental effects. The highest correlation was found between depression and adolescent suicide [44].

Genetic association studies using various candidate genes with adolescent suicidal behavior, including attempt, completed suicide and ideation have been looked into. Several candidate genes and pathways have been investigated with a focus on neurotransmitters, neurotrophic processes, stress response system, and the immune system. Results suggest the serotonergic system to be the most plausible system explaining anxiety, impulsivity, depressed mood, and adolescent suicidal behavior. However, inconsistencies for serotonergic genes were also reported for adolescent suicidal behavior which largely reflected the ethnic and phenotypic variation.

Details of each study, including the study design, sample characteristics, genetic variant and salient findings are shown in Table-1. A narrative review of the literature, including all the 17 studies was done and is given below.

Table-1: Genetic studies on adolescent suicide

No.	Study method	Study sample	Gene (variant) / trait	Findings	Population	Reference
1	Family study	203 first- and 607 second-degree relatives of 58 adolescent suicide probands and 207 first- and 558 second-degree relatives of 55 demographically similar controls.	Familial trait of suicidal behavior, independent of psychiatric disorders	Increased suicide attempts in the first-degree relatives of suicide probands. Higher ratings of aggression were associated with higher familial loading for suicide attempts.	Western Pennsylvania	Brent DA et al, 1996 [17]
2	Family study	Relatives of 62 clinically referred adolescent suicide attempters and 70 never-suicidal psychiatric controls	Familial aggregation of adolescent suicide attempts and personality disorders and aggression	Familial Personality disorder was significantly associated with suicidal risk. Relationship between proband assaultiveness and familial aggregation of suicidality observed.	United States	Johnson BA et al, 1998 [36]
3	Family based & Case Control methods	88 adolescent patients admitted with recent suicide attempt; 40 family trios; 12 family duos. 172 healthy subjects for the case control design.	Tryptophan hydroxylase A218C polymorphism	No significant association	Jewish	Zalsman G et al, 2001 [37]
4	Haplotype relative risk (HRR) calculation	48 inpatient adolescents	The serotonin transporter (5- <i>HTTLPR</i>)	No significant association. Significant difference in violence measures between "LL" and "LS" genotypes	Israel	Zalsman G et al, 2001a [38]
5	Case Control study	69 inpatient of adolescents suicide attempters and 167 healthy controls	Dopamine receptor subtype 4 (<i>DRD4</i>) 48 bp VNTR	No significant association. Significant difference in depression severity between suicidal inpatients homozygote and heterozygote for the <i>DRD4</i> alleles observed.	Israel	Zalsman G et al, 2004 [39]
6	Family- based method	32 families of adolescents suicide attempters where parents of the study patients served as the control group.	5- <i>HTR2A</i> (T102C)	No significant association	Jewish Ashkenazi	Zalsman G et al, 2005 [40]

7	Comparative study	32 suicidal and 28 non-suicidal adolescent psychiatric inpatients	5-HTTLPR and platelet transporter binding	No association found. Positive correlation between platelet SERT density and anger scores and negative correlation between platelet count and trait anxiety observed.	Israel Ashkenazi	Zalsman G et al, 2005a [41]
8	Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial	155 treatment-resistant depressed adolescents	FKBP5	FKBP5 (rs1360780 "TT", rs3800373"GG" genotype) with suicidal events even after controlling for treatment effects.	European	Brent DA et al, 2010 [42]
9	Multi-centre study	35 suicidal and 30 non-suicidal adolescent inpatients, 51 adolescent suicide attempters admitted to psychiatric emergency rooms and a community-based control group (N = 95)	HTR2A (T102C), 5-HTTLPR, MAOA, and plasma serotonin	Homozygous "TT" genotype of the HTR2A 102T/C with lower impulsivity and aggression. Low activity MAOA genotypes with suicidality. 5-HTTLPR and plasma serotonin levels showed no association.	Jewish, Ethiopian, Yemenite, Arabs and mixed origin	Zalsman G et al, 2011 [43]
10	Twin study	2814 twins from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) and young adult follow-up (YAFU)	Familial aggregation of suicidal ideation, depression & conduct disorder	Highest correlations were between depression and suicide within adolescence (62). The lowest correlations were between juvenile depression and young adult suicidal ideation (27) and between juvenile conduct disorder and suicidal ideation in young adulthood (19). There was a moderate correlation between adolescent and young adult suicide ideation (45)	Virginia Caucasian	Linker J et al, 2012 [44]
11	Observational study (Preliminary investigation)	76 hospitalized adolescents	DRD4 VNTR	DRD4 "L" carriers with a sexual trauma history had more severe suicidal ideation	Northeastern United States	Doorley J et al, 2017 [45]
12	Case Control study	98 adolescent suicide attempters who required hospitalization based on emergency assessments, and 150 healthy volunteers	COMT, CRHR1, FKBP5, SLC6A4, HTR1B, HTR2A, TPH1, TPH2, BDNF, NTRK2, NOS1, IL28RA	NTRK2 (rs10868235, rs1659400), NOS1 (rs2682826) and TPH2 (rs7305115) with suicide attempts & quantitative hopelessness or impulsivity scores.	CEU countries	Mirkovic et al, 2017 [46]

13	RNA sequencing in post mortem brain samples	Age > 13 years;Suicides by violent means(n=65), non-violent suicides(n=46),non-violent non suicides (n=78) & healthy subjects with trait aggression	<i>LINC01268</i> (Human -specific long intergenic non coding RNA)	Prefrontal expression of <i>LINC01268</i> was higher in suicides by violent means, emotional regulation and aggressive behavior.	Caucasian	Punzi G et al,2019 [47]
14	Case Control study	200 adolescents with depression and suicide attempt &235 controls	<i>5-HTTLPR</i>	<i>5-HTTLPR</i> "SS" genotype with the history of depression and suicide attempt in adolescents	Mexican	Sarmiento-Hernández et al, 2019 [48]
15	Prospective, population-based twin study	30,444 children at 9 or 12 years and 10,269 adolescents re- assessed at age 18 years	Association between general psychopathology during childhood and adolescent SA/SH.	General factor of psychopathology in childhood was a statistically significant predictor of adolescent suicide attempt.Shared genetic overlap may occur between the two factors.	Sweden	O'Reilly LM et al, 2020 [49]
16	Prospective longitudinal family study of third generation offspring	478 children;330 of them continued follow-up till young adulthood(>19 years)	<i>ANKK1</i> , <i>DRD2</i> , <i>COMT</i> , <i>SLC6A4</i> , <i>HTR2C</i>	<i>ANKK1</i> (rs1800497), <i>HTR2C</i> (rs6318) , <i>ANKK1-DRD2</i> complex (AAACHaplo type) and <i>HTR2C</i> (CCC haplo type) presence and onset of child/adolescent suicidal ideation.	United States	Hill SY et al, 2020 [50]
17	Case Control study	97 adolescents diagnosed with major depressive disorder & 106 controls	<i>LEPR</i> (Leptin receptor)	<i>LEPR</i> (rs1171276) with the suicide probability scores in depressed adolescents	Turkey	Acikel BS et al, 2020 [51]

Initial literature on the familial trait of adolescent suicidal behavior came from Brent et al (1996) who studied 810 relatives of 58 adolescent suicide victims and 765 relatives of 55 adolescent controls [17]. After adjusting for differences in familial psychiatric disorders, the study reported that the rates of suicide attempts in first-degree relatives of the suicide victims were more (odds ratio 4.3) [17]. Similar familial aggregation of adolescent suicidal behavior was later reported for the presence of familial personality disorder and proband assaultiveness [36]. Significantly higher rates of suicide attempts and completion were observed in the first-degree relatives of adolescent attempters with higher scores on assault subscales of the Buss-Durkee Hostility Inventory [36]. Familial aggregation of depression and suicide has also been reported from the Virginia Twin Study of Adolescent Behavioral Development, involving 2814 twins [44]. A population based twin study from Sweden reported that the general factor of psychopathology in childhood was a significant predictor of adolescent suicide attempts as compared with other factors of inattention, impulsivity, anxiety, emotional symptoms, or oppositional behavior [49].

The major contributions to the understanding of the genetics of adolescent suicide came from the studies by Zalsman's group. First study was on an ethnically homogeneous group of Jewish origin, comprising of both families based on 40 family trios, 12 family duos and, a case-control method using 88 adolescents with a recent suicide attempt, and 172 healthy controls. The first study in 2001 explored the A218C variant in intron 7 of Tryptophan hydroxylase (*TPH*) gene and 5-HydroxyTryptamine Transporter Gene-Linked Polymorphic Region (*5-HTTLPR*) in adolescent suicide attempt [37,38]. They used haplotype relative risk (HRR) and the transmission disequilibrium test (TDT) methods and did not find any significant association of the A218C *TPH* polymorphism with suicide attempt (P=0.76 by HRR method and P=0.61 by TDT method) [37]. They also did not find any significant allelic association with *5-HTTLPR* for adolescent suicidal

behavior ($p > 0.05$). However, measurements of violence showed a significant difference ($P = 0.029$) between adolescents having “LL” and “LS” genotypes [38]. Almost a similar lack of significant observations was reported with dopamine receptor subtype 4 (*DRD4*) gene exon III 48 bp repeat polymorphism in a case-control study by the same team. However, the authors observed a significant difference in depression severity among those homozygous and heterozygous for the *DRD4* allele [39]. Within the suicidal group ($n = 32$), platelet serotonin transporter density showed a significant positive correlation with anger scores ($r = 0.40$; $p = 0.027$), and platelet count showed a negative correlation with trait anxiety ($r = 0.42$; $p = 0.034$) but no association was observed between *5-HTTLPR* variants and suicidality or platelet transporter binding [41]. Family-based studies did not reveal any association of the T102C5-Hydroxy Tryptamine Receptor 2A gene variant (*5-HTR2A*) with clinical variables like depression and impulsive-aggressive traits [40]. The same group using serotonergic and adrenergic candidate gene variants of *HTR2A*, *5HTTLPR*, and Monoamine Oxidase A, (*MAOA*) in a multicenter study comprising of Jewish, Ethiopian, Yemenite, Arab, and mixed origin population, carried out an association study with clinical phenotypes of adolescent suicidality, psychopathology, and aggression. The study sample included suicidal, non-suicidal, those with recent suicide attempts, and community-based controls. All the subjects were genotyped, and measurements of plasma serotonin content were taken and relevant psychological domains, like impulsivity, aggression, and anxiety were also assessed. The group reported that the homozygous “TT” genotype of the *HTR2A* 102T/C variant was associated with lower impulsivity ($P = 0.03$) and aggression ($P = 0.01$) and this finding was in contrast to the results from earlier studies. Suicidality was also reported to be associated with low activity *MAOA* genotypes ($P = 0.04$). However, plasma serotonin levels did not show any association with these variants [43].

Another study explored whether the carrier status of the Dopamine D4 Receptor (*DRD4*) variable number of tandem repeat (VNTR) polymorphism affected the connection between sexual trauma and suicidal behavior in an adolescent inpatient sample (n=76). *DRD4* VNTR variant was significantly associated with severe suicidal ideation in *DRD4*“L” carriers with a sexual trauma history when compared to *DRD4* “SS” homozygotes, while suicide attempts did not show any such interaction [45].

Mirkovic and team did an extensive study of 22 SNPs in about a dozen genes [Catechol-o-methyl transferase gene (*COMT*), Corticotropin-releasing hormone receptor 1 gene (*CRHR1*), gene encoding FK 506 binding protein 5 (*FKBP5*), solute carrier family 6 members 4 or serotonin transporter gene (*SLC6A4*), serotonin receptor genes (*HTR1B*, *HTR2A*), tryptophan hydroxylase gene (*TPH1*, *TPH2*), brain-derived neurotrophic factor gene (*BDNF*), neurotrophic tyrosine kinase gene (*NTRK2*), nitric oxide synthase1 gene (*NOS1*) and interleukin28receptor alpha-subunit gene(*IL28RA*)] with attempts to suicide, hopelessness and impulsivity in a European adolescent inpatient sample of suicide attempters (n=98), and 150 healthy volunteers. They report significant associations with suicide attempts were rs10868235, rs1659400 (*NTRK2*), rs2682826(*NOS1*), and rs7305115(*TPH2*) and some of these variations also showed association with clinical phenotypes of hopelessness or impulsivity. However, they caution that the small sample size and possible gene-environment interactions could also have affected the results [46].

The *FKBP5* gene that codes for a protein-producing glucocorticoid receptor sub-sensitivity was studied by Brent et al in a group of adolescents with antidepressant-resistant depression. The study reported a significant association with rs1360780 “TT” genotypes and rs3800373G allele of the *FKBP5* gene with suicidal events, even after controlling for other relevant variables including treatment effects. It was also seen that the linkage disequilibrium between these two SNPs was

significant ($r=0.91$). They report that glucocorticoid receptor sub-sensitivity caused by these SNPs may suggest the link between hypothalamic-pituitary-adrenal (HPA) axis changes and suicidality [42].

Another unique and interesting observation came from RNA sequencing data of Long Intergenic Non-Coding RNA (*LINC01268*) of post mortem brain samples on violent suicides in adolescents followed up with an evaluation of a genetic variant in *LINC01268* associated with altered expression in healthy subjects with trait aggression and prefrontal physiology related to behavioral control. *LINC01268* was differentially expressed with higher expression in the prefrontal brain areas in suicides by violent means when compared to both non-suicides and suicides by nonviolent means. Aggression scores were found to be higher in a living cohort with the same risk genotypes ($P=0.01$). In these subjects, functional neuroimaging was performed while viewing angry faces interestingly they show reduced prefrontal engagement (Brodmann area 10). The authors concluded that these results suggest the influence of *LINC01268* in the regulation of emotion, aggression, and violent suicide. Weighted gene co-expression network analysis indicated modulation of genes involved in the immune response [47].

A recent case-control study in 2019, on 200 Mexican adolescents with clinical depression and suicide attempts and 235 healthy controls, showed that statistically, a significant difference existed between the frequencies of ss genotypes ($p=0.004$) and (s) allele ($p=0.0009$) of the 5-*HTTLPR* variant among the groups. The findings suggest that these genetic variants may be related to adolescent depression and suicide attempts [48].

A prospective longitudinal family study involving three generations, among 478 participants, based on varying family history (high vs low) for alcohol and other substance use disorders was carried out by Hill et al. (2020) [50]. The subjects included third-generation children/ adolescents

between the ages of 8-18 years who were assessed repeatedly until age 19. Out of this sample, a further follow-up of 330 individuals to young adulthood was done to look for the emergence of depression. Clinical assessment of aggression, using Child Behavior Checklist (CBCL) aggression scale scores brought out significant association with child/adolescent suicidal ideation. Two SNPs rs1800497 in the ankyrin repeat and kinase domain containing 1 gene (*ANKK1* gene), and rs6318 in the *HTR2C* gene, and two haplotypes (AAAC in the *ANKK1-DRD2* complex, and CCC in the *HTR2C* gene), were found to be significantly associated with the presence and onset of adolescent suicidal ideation. Assessments in young adulthood showed that adolescent suicide ideation had a significant association with young adult depression [50].

The latest case-control study comprising of 97 adolescents (between the age of 12 and 18 years) with major depressive disorder and 106 controls was reported in Turkish adolescents with leptin receptor (*LEPR*) variant and adolescent suicidal behavior by Acikel et al. [51] Linear regression analysis showed that the leptin receptor polymorphism rs1171276 had an association with suicidal behavior, in depressed adolescents ($B=4.346$ $t=2.220$ $P=0.048$). Depressive scores (by Children Depression inventory) were significantly predicted by a family history of depression ($P<0.0001$, $OR= 4.2$) and the number of stressful life events ($P=0.001$, $OR= 1.7$). The study concluded that the *LEPR* variant may lead to higher adolescent impulsive behavior and suicide probability scores, through leptin resistance [51].

Discussion

Though suicidal behavior among adolescents is a global concern, the genetic studies in this area have been sparse. It has been cited that the difficulty in getting genetic research consent for minors could be a possible reason [19]. The large heterogeneity of suicidal behavior is a big challenge to those exploring the underlying genetic mechanisms. The contributions from gene, environment,

and potential gene-environment interactions need to be considered. Genetic association studies detecting small effects are considered useful, as multiple genes are known to contribute to small modulation of suicidal risk. Research on suicidal behavior is mostly based on the hypothesis of “common-disease common variant” [19].

Study Design

Studies on the genetic dissection of suicidal behavior in adolescent children have followed different study design that involves family-based, case-control, or population-based design strategies. Family-based studies are common in genetic research. Many researchers claim this method to be advantageous over case-control association studies, as they yield lower false-positive and false-negative results [52]. Methods employed include the haplotype relative risk (HRR) and the transmission disequilibrium test (TDT). The HRR method examines samples based on “trios” of the affected child and both biological parents [53]. In this method, a comparison is made between the alleles transmitted to the patient from the parents with the non-transmitted alleles, which are taken as controls. Sometimes, parent-child duos may be assessed if only one parent is available. HRR has the advantage of utilizing smaller samples than the case-control design [53]. The TDT is another useful method where linkage disequilibrium is examined through transmitted versus non-transmitted alleles from heterozygote parents [54]. Though many family-based studies exploring the genetics of adolescent suicide have been done, results have been contradictory and no single locus was found to be significantly associated with adolescent suicidality [35].

Serotonergic genes

Data from various studies suggest the serotonergic system as the most relevant neurobiological system connected to impulsivity, anxiety, and adolescent suicidal behavior[4,35,43].Tryptophan hydroxylase (*TPH*) which is the rate-limiting enzyme involved in serotonin (5-HT) synthesis,

serotonin transporter (*5-HTT*) which regulates 5-HT signaling at the synapses, and serotonin receptors (from *5-HT1* to *5-HT7* with several subtypes and isoforms *5-HT1A*, *5-HT2A*, and others) have been the focus of study over time. Zalsman and colleagues found no significant association for most of the serotonergic genes among Jewish adolescents. However, in a recent multicentric study with a genetically heterogeneous sample, Zalsman and colleagues reported homozygosity (TT) for the serotonin receptor polymorphism was associated with lower impulsivity and aggression [43]. Postmortem brain studies of teenage suicide victims showed higher expression of serotonin 5-HT_{2A} receptors in the prefrontal cortex [55].

The serotonin transport gene, *SLC6A4* is situated on chromosome 17 (17q11.2). The common functional genetic variation (*5-HTTLPR*, rs4795541), consists of a short (s) and a long allele (l). The efficiency of the L allele to transcribe the genes two to three times more than the S allele [56]. Different research teams have studied this candidate gene in detail, yielding divergent results. Zalsman and team reported that 5-HTTLPR polymorphism did not have any significant association with adolescent suicidality [38]. Sarmiento-Hernández et al showed that 5-HTTLPR polymorphism (S allele and the SS genotype) were related to a history of depression and suicide attempts in Mexican adolescents [48]. Caspi et al found that subjects who were carriers of the S allele of the 5-HTTLPR polymorphism reported more depressive symptoms and suicidality about stressful life events, especially among adolescents and young adults [57].

Dopaminergic receptors

The association of dopaminergic receptor gene polymorphism and adolescent suicide was explored by several investigators with contrasting observations. One study investigating the role of Dopamine receptor subtype 4 (*DRD4*) gene exon III 48 bp repeat polymorphism did not show any significant association with adolescent suicidal behavior [39]. Contrast the same VNTR

carrying *DRD4* (L) carriers with an antecedent sexual trauma reported significantly more severe suicidal ideation [45]. A study with *DRD2-ANKK1* region suggested a potential association in a study comparing a group of children, with high or low familial risk for alcohol dependence. The haplotype AAAC in this region was significantly associated with suicidal ideation. The SNP rs1800497 of the *ANKK1* gene also exhibited a strong association with suicidal ideation, this significance was not altered in the survival model, even after taking familial alcohol dependence as a covariate [50].

Metabolism of catecholamines

Catecholamine degradation is mainly done by Catechol-O-methyltransferase (*COMT*). The enzyme is encoded by a single gene located on chromosome 22q11.1-q11.2. Another enzyme involved in neurotransmitter (serotonin, dopamine, and norepinephrine) degradation is monoamine oxidase A (*MAOA*). A large majority of the studies were on adult suicide; however, few have studied adolescent suicide. Catechol-O-methyltransferase variation showed no association with suicidal ideation among children/adolescents unlike adult suicide [50]. Another study has shown that *MAOA* genotypes with less activity were associated with suicidal behavior among adolescents [43].

Hypothalamic-Pituitary-Adrenal axis

Blunted HPA axis activity, especially among individuals with psychopathology may reduce the ability to respond adaptively to ongoing stressors and may increase the suicidal risk [58]. As part of the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial in a group of European adolescents (n=155), rs1360780TT and rs3800373G SNPs of the *FKBP5* gene were reported to be associated with suicidal events, even after controlling for treatment effects and other

relevant variables. The glucocorticoid receptor sub-sensitivity caused by these variations may be the link between the alterations in the HPA axis and suicidal behavior [42].

Genes associated with neurotrophic processes

Though genes engaged in neurotrophic processes have been proposed to have a role in suicidal behavior, very few studies have been done among adolescents. A low level of brain-derived neurotrophic factor (*BDNF*), obstructs the normal development of serotonin neurons during brain development and this may lead to adolescent suicidal behavior [59]. Two variants, rs10868235 and rs1659400 on the neurotrophic receptor kinase (*NTRK2*) gene, showed significant associations for adolescent suicide attempts. However, this association did not stand the statistical correction tests and the authors concluded that the role of these SNPs was not supported in adolescent suicide attempts and cited small sample size and gene-environment interactions as possible confounders [46].

Other genes

Impulsivity and aggression are suggested as behavioral substrates for adolescent suicidal behavior. Leptin receptor gene polymorphism may lead to an increase in impulsive behavior and adolescent suicidal behavior. A recent study has identified an association between rs1171276 SNP of the leptin receptor and the suicide probability scores among adolescents with depression [51]. Prefrontal expression of long intergenic noncoding RNA (*LINC01268*) was found to be higher in suicides by violent means, when compared to no suicides and suicides by nonviolent means, highlighting its role in emotional regulation, aggressive behavior, and violent suicide. Further network analysis suggested the underlying biological mechanism to be the modulation of genes involved in the immune response [47].

Genetic observations on adolescent suicidal behavior are sparse but hint at several candidate genes that associate with various pathways. A large majority of the results are preliminary or inconsistent, probably due to the smaller sample size or the effects of interaction (gene-gene interaction or gene-environment) on suicidal behavior [46]. Existing psychopathology may have been a potential confounder and may have influenced the findings. It had been opined that for properly controlling psychopathology, studies have to compare subjects who committed suicide and those who had other causes of death within the same psychopathological group. To find such a group may be practically difficult [60]. Gene-environment interactions have largely been pointed out in the case of stressful life events leading to suicidal behavior. It has also been reported that the timing is critical in understanding the gene, environment, and timing interactions in adolescent suicidal behavior [9]. During the critical period of adolescent brain development, suicidality may occur when particular genotypes are exposed to specific environment-related risks [9]. Little focus was given to this combined gene-environment interaction and timing, in research done so far. Follow-up studies were few [50] and the literature search did not yield any genome-wide studies done on adolescent suicide.

Available literature has several limitations. The majority of the studies had a small sample size and different genetic variants were studied which may have led to diverse observations. Heterogeneity in the definition of suicidal behavior, ideation, and the attempt was another significant variable that needs to be controlled. The limitation exists concerning extrapolating the results of an ethnically homogeneous population to other population groups. In this review, an extensive and thorough comparison with the genetics of adult suicidal behavior was not attempted, as the studies are numerous and recent review articles are available. Technological considerations of individual studies were also not made.

To conclude, genetic research on adolescent suicidal behavior has been sparse. Though a strong genetic component has been identified, there is no consensus on specific genetic markers for adolescent suicidal behavior. Association studies have brought out the likely candidate genes and various neurobiological pathways contributing to the behavior. Gene-gene, gene-environment interactions, and the timing of these interactions seem to affect adolescent suicidality. Different candidate genes were explored by different research teams, and this may have led to diverse observations. Hence it becomes important to focus future research on the same genetic variants or plan a genome-wide study to find the significant associations. Advances in genetic and statistical methodologies may bring in even more consistent findings. Future research may incorporate these changes. Considering the huge global public health issue of adolescent suicide, it is important to conduct more research for better understanding of the underlying genetic factors and their interaction with other genetic and non-genetic factors. It will further help in effective identification, prevention, and management of adolescent suicidal behavior.

Acknowledgements: Nil

Conflicts of Interest: Nil

References

1. McKinnon B, Gariépy G, Sentenac M, Elgar FJ. Adolescent suicidal behaviours in 32 low- and middle-income countries. *Bull World Health Organ.* 2016, 94(5):340-350.
2. Patton GC, Coffey C, Sawyer SM, Viner RM, Haller DM, Bose K, et al. Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet.* 2009, 374(9693):881-92.
3. National Institute of Mental Health. Suicide.[cited 2020 Sept 18]. Available from:URL: https://www.nimh.nih.gov/health/statistics/suicide.shtml#part_155013
4. Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci.* 2003, 4(10):819-28.

5. Cha CB, Franz PJ, M Guzmán E, Glenn CR, Kleiman EM, Nock MK. Annual Research Review: Suicide among youth - epidemiology, (potential) etiology, and treatment. *J Child Psychol Psychiatry*. 2018, 59(4):460-482.
6. Grunbaum JA, Kann L, Kinchen S, Ross J, Hawkins J, Lowry R, et al. Youth risk behavior surveillance--United States, 2003. *MMWR SurveillSumm*. 2004, 53(2):1-96.
7. Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet*. 2016, 387(10024):1227-39.
8. Brent DA, Mann JJ. Family genetic studies, suicide, and suicidal behavior. *Am J Med Genet C Semin Med Genet*. 2005, 133C(1):13-24.
9. Zalsman G. Timing is critical: gene, environment and timing interactions in genetics of suicide in children and adolescents. *Eur Psychiatry*. 2010, 25(5):284-6.
10. EssexMJ, BoyceWT, HertzmanC, LamLL, ArmstrongJM, NeumannSM, et al. Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. *Child Dev*. 2013, 84:58-75.
11. Jokinen J, Boström AE, Dadfar A, Ciuculete DM, Chatzittofis A, Åsberg M, et al. Epigenetic changes in the CRH gene are related to severity of suicide attempt and a general psychiatric risk score in Adolescents. *EBioMedicine*. 2018, 27:123-133.
12. Brent DA, Melhem N. Familial transmission of suicidal behavior. *Psychiatr Clin North Am*. 2008, 31(2):157-77.
13. Althoff RR, Hudziak JJ, Willemsen G, Hudziak V, Bartels M, Boomsma DI. Genetic and environmental contributions to self-reported thoughts of self-harm and suicide. *Am J Med Genet B Neuropsychiatr Genet*. 2012, 159B(1):120-7.
14. Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, et al. Suicidal behaviour: an epidemiological and genetic study. *Psychol Med*. 1998, 28(4):839-55.
15. Fu Q, Heath AC, Bucholz KK, Nelson EC, Glowinski AL, Goldberg J, et al. A twin study of genetic and environmental influences on suicidality in men. *Psychol Med*. 2002, 32(1):11-24.
16. Roy A, Segal NL, Centerwall BS, Robinette CD. Suicide in twins. *Arch Gen Psychiatry*. 1991, 48(1):29-32.
17. Brent DA, Bridge J, Johnson BA, Connolly J. Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. *Arch Gen Psychiatry*. 1996, 53(12):1145-52.

18. Turecki G. The molecular bases of the suicidal brain. *Nat Rev Neurosci*. 2014, 15(12):802-16.
19. Mirkovic B, Laurent C, Podlipski MA, Frebourg T, Cohen D, Gerardin P. Genetic Association Studies of Suicidal Behavior: A Review of the Past 10 Years, Progress, Limitations, and Future Directions. *Front Psychiatry*. 2016, 23;7:158.
20. Fergusson DM, Woodward LJ, Horwood LJ. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychol Med*. 2000, 30(1):23-39.
21. Brezo J, Klempan T, Turecki G. The genetics of suicide: a critical review of molecular studies. *Psychiatr Clin North Am*. 2008, 31(2):179-203.
22. Afifi TO, Enns MW, Cox BJ, Asmundson GJ, Stein MB, Sareen J. Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *Am J Public Health*. 2008, 98(5):946-52.
23. Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci*. 2012, 35(1):14-23.
24. Melhem NM, Brent DA, Ziegler M, Iyengar S, Kolko D, Oquendo M et al. Familial pathways to early-onset suicidal behavior: familial and individual antecedents of suicidal behavior. *Am J Psychiatry*. 2007, 164(9):1364-70.
25. Shaffer D. The epidemiology of teen suicide: an examination of risk factors. *J Clin Psychiatry*. 1988, 49 Suppl:36-41.
26. Brent DA. Risk factors for adolescent suicide and suicidal behavior: mental and substance abuse disorders, family environmental factors, and life stress. *Suicide Life Threat Behav*. 1995, 25 Suppl:52-63.
27. Turecki G. Dissecting the suicide phenotype: the role of impulsive-aggressive behaviours. *J Psychiatry Neurosci*. 2005, 30(6):398-408.
28. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. *Dev Psychobiol*. 2010, 52(7):671-90.
29. Perroud N, Paoloni-Giacobino A, Prada P, Olié E, Salzmann A, Nicastro R et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. *Transl Psychiatry*. 2011, 13;1(12):e59.

30. McGowan PO, Roth TL. Epigenetic pathways through which experiences become linked with biology. *Dev Psychopathol.* 2015, 27(2):637-48.
31. Labonté B, Suderman M, Maussion G, Navaro L, Yerko V, Mahar I, Bureau A et al. Genome-wide epigenetic regulation by early-life trauma. *Arch Gen Psychiatry.* 2012, 69(7):722-31.
32. Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry.* 1999, 156(2):181-9.
33. Vargas-Medrano J, Diaz-Pacheco V, Castaneda C, Miranda-Arango M, Longhurst MO, Martin SL, et al. Psychological and neurobiological aspects of suicide in adolescents: Current outlooks. *Brain Behav Immun Health.* 2020, 7:100124.
34. Hawton K, van Heeringen K. Suicide. *Lancet.* 2009, 373(9672):1372-81.
35. Zalsman G. Genetics of Suicidal Behavior in Children and Adolescents. In: Dwivedi Y, editor. *The Neurobiological Basis of Suicide.* Boca Raton (FL): CRC Press/Taylor & Francis, 2012.
36. Johnson BA, Brent DA, Bridge J, Connolly J. The familial aggregation of adolescent suicide attempts. *Acta Psychiatr Scand.* 1998, 97(1):18-24.
37. Zalsman G, Frisch A, King RA, Pauls DL, Grice DE, Gelernter J, et al. Case control and family-based studies of tryptophan hydroxylase gene A218C polymorphism and suicidality in adolescents. *Am J Med Genet.* 2001, 105(5):451-7.
38. Zalsman G, Frisch A, Bromberg M, Gelernter J, Michaelovsky E, Campino A, et al. Family-based association study of serotonin transporter promoter in suicidal adolescents: no association with suicidality but possible role in violence traits. *Am J Med Genet.* 2001, 105(3):239-45.
39. Zalsman G, Frisch A, Lewis R, Michaelovsky E, Hermesh H, Sher L et al. DRD4 receptor gene exon III polymorphism in inpatient suicidal adolescents. *J Neural Transm(Vienna).* 2004, 111(12):1593-603.
40. Zalsman G, Frisch A, Baruch-Movshovits R, Sher L, Michaelovsky E, King RA et al. Family-based association study of 5-HT(2A) receptor T102C polymorphism and suicidal behavior in Ashkenazi inpatient adolescents. *Int J Adolesc Med Health.* 2005, 17(3):231-8.

41. Zalsman G, Anderson GM, Peskin M, Frisch A, King RA, Vekslerchik M et al. Relationships between serotonin transporter promoter polymorphism, platelet serotonin transporter binding and clinical phenotype in suicidal and non-suicidal adolescent inpatients. *J Neural Transm (Vienna)*. 2005, 112(2):309-15.
42. Brent D, Melhem N, Ferrell R, Emslie G, Wagner KD, Ryan N, et al. Association of FKBP5 polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. *Am J Psychiatry*. 2010, 167(2):190-7.
43. Zalsman G, Patya M, Frisch A, Ofek H, Schapir L, Blum I, et al. Association of polymorphisms of the serotonergic pathways with clinical traits of impulsive-aggression and suicidality in adolescents: a multi-center study. *World J Biol Psychiatry*. 2011, 12(1):33-41.
44. Linker J, Gillespie NA, Maes H, Eaves L, Silberg JL. Suicidal ideation, depression, and conduct disorder in a sample of adolescent and young adult twins. *Suicide Life Threat Behav*. 2012, 42(4):426-36.
45. Doorley J, Williams C, Mallard T, Esposito-Smythers C, McGeary J. Sexual Trauma, the Dopamine D4 Receptor, and Suicidal Ideation Among Hospitalized Adolescents: A Preliminary Investigation. *Arch Suicide Res*. 2017, 21(2):279-292.
46. Mirkovic B, Cohen D, Laurent C, Lasfar M, Marguet C, Gerardin P. A case-control association study of 12 candidate genes and attempted suicide in French adolescents. *Int J Adolesc Med Health*. 2017, 32(1):/j/ijamh.2020.32.issue-1/ijamh-2017-0089/ijamh-2017-0089.xml.
47. Punzi G, Ursini G, Viscanti G, Radulescu E, Shin JH, Quarto T et al. Association of a Noncoding RNA Postmortem With Suicide by Violent Means and In Vivo With Aggressive Phenotypes. *Biol Psychiatry*. 2019, 85(5):417-424.
48. Sarmiento-Hernández EI, Ulloa-Flores RE, Camarena-Medellín B, Sanabrais-Jiménez MA, Aguilar-García A, Hernández-Muñoz S. Association between 5-HTTLPR polymorphism, suicide attempt and comorbidity in Mexican adolescents with major depressive disorder. *ActasEspPsiquiatr*. 2019, 47(1):1-6.
49. O'Reilly LM, Pettersson E, Quinn PD, Klonsky ED, Lundström S, Larsson H, et al. The association between general childhood psychopathology and adolescent suicide attempt

- and self-harm: A prospective, population-based twin study. *J Abnorm Psychol.* 2020, 129(4):364-375.
50. Hill SY, Jones BL, Haas GL. Suicidal ideation and aggression in childhood, genetic variation and young adult depression. *J Affect Disord.* 2020, 276:954-962.
 51. Acikel SB, Eroglu C, UgrasDikmen A, Kurar E. The association between leptin receptor polymorphism and suicidal behaviour in depressed adolescents. *Int J Psychiatry ClinPract.* 2020, 24(2):120-126.
 52. Schaid DJ, Sommer SS. Comparison of statistics for candidate-gene association studies using cases and parents. *Am J Hum Genet.* 1994, 55(2):402-9.
 53. Ott J. Statistical properties of the haplotype relative risk. *Genet Epidemiol.* 1989, 6(1):127-30.
 54. Spielman RS, Ewens WJ. The TDT and other family-based tests for linkage disequilibrium and association. *Am J Hum Genet.* 1996, 59(5):983-9.
 55. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Pandey SC, Pesold C et al. Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. *Am J Psychiatry.* 2002, 159(3):419-29.
 56. Heils A, Teufel A, Petri S, Stöber G, Riederer P, Bengel D, et al. Allelic variation of human serotonin transporter gene expression. *J Neurochem.* 1996, 66(6):2621-4.
 57. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003, 301(5631):386-9.
 58. Melhem NM, Keilp JG, Porta G, Oquendo MA, Burke A, Stanley B, et al. Blunted HPA Axis Activity in Suicide Attempters Compared to those at High Risk for Suicidal Behavior. *Neuropsychopharmacology.* 2016, 41(6):1447-56.
 59. Sher L. The role of brain-derived neurotrophic factor in the pathophysiology of adolescent suicidal behavior. *Int J Adolesc Med Health.* 2011, 23(3):181-5.
 60. Turecki G. Dissecting the suicide phenotype: the role of impulsive-aggressive behaviours. *J Psychiatry Neurosci.* 2005, 30(6):398-408.

Dr. Anju Mathew, Associate Professor, Department of Psychiatry, Government Medical College, Thiruvananthapuram, Dr. Naresh Nebhinani, Additional Professor, Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), Jodhpur, Dr. Saboora Beegum, Professor, Dept. of

Biochemistry, Government Medical College, Calicut, Dr. Vijayakumar K, Associate Professor,
Department of Community Medicine, Amritha School of Medicine, Kochi, Dr. Moinak Banerjee,
Scientist G, Human Molecular Genetics Laboratory, Rajiv Gandhi Centre for Biotechnology,
Thiruvananthapuram