Genome Medicine

REVIEW

Genetics of childhood and adolescent depression: insights into etiological heterogeneity and challenges for future genomic research

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Abstract

There is heterogeneity between depression in childhood, adolescence and adulthood in terms of the gender composition of affected cases, prevalence, rates of recurrence and risk factors. This raises complex questions for refining the phenotype for molecular genetic studies of depression and the selection of appropriate proband groups. This article aims to provide a review of issues arising from family, twin and adoption studies of relevance to molecular genetic studies, and to summarize molecular genetic findings on childhood/adolescent depression. While retrospective studies of adults suggest greater familial aggregation among those with an earlier age of onset, prospective studies do not confirm this association. In fact, taken together, evidence from family and twin studies suggests that prepubertal depression is more strongly associated with psychosocial adversity, is less heritable and shows lower levels of continuity with adult depression than either adolescent or adult depression. Adolescent depressive symptoms and disorder show similar levels of heritability to depression in adult life, although there is only one twin study of adolescent depressive disorder, and heritability estimates of depressive symptoms vary widely between studies. This variability in heritability estimates is partly attributable to age and informant effects. Adoption studies and other intergenerational transmission designs show that the transmission of depression between parents and children involves genetic and environmental processes, with converging evidence that environmental processes are most important. Molecular genetic studies of childhood/adolescent depression have to date used a candidate gene approach and focused on genes already examined in adult studies. Prospective longitudinal studies of community and high-risk samples are needed to clarify issues of etiological heterogeneity in depression, and these should in turn inform the planning of molecular genetic studies.

Prevalence and clinical significance of childhood and adolescent depression

Major depressive disorder (MDD) during childhood is relatively uncommon and the 12-month prevalence ranges from 0.5% to 3% [1,2], with an equal proportion of girls and boys affected or a slight preponderance of boys. Adolescence is a period of vulnerability for depressive disorder with first onsets often occurring during this period and subthreshold symptoms increasing markedly [3-5]. Estimates of the 12-month prevalence of depressive disorder in adolescence range from 2% to 8%, and the figure for lifetime adolescent depression is 20% [1,2,6]. In adolescence, the ratio of affected females to males is 2:1, which mirrors the pattern seen in adult life [2,6]. Adolescent subthreshold symptoms are not benign, and high levels of depressive symptoms that fall below the diagnostic threshold are associated with functional impairment [7]. Depression interferes with the ability of young people to meet their academic, economic and social potential, and is associated with a greatly increased risk of suicide and suicidal behaviour [1]. A significant proportion of depressed adolescents continue to have mental health problems and poor social outcomes in adult life [8].

Features of childhood/adolescent depression compared with adult depression

The criteria used to diagnose depression in children and adolescents are the same as those used in adults, with the only exception being that the Diagnostic and Statistical Manual of Mental Disorders criteria allow irritable mood

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instead of depressed mood as a core symptom for children and adolescents [9]. The fact that the same criteria are used to diagnose depression in childhood/adolescence and adulthood implicitly assumes similarity in the presentation of depression across developmental stages. Although very few studies have compared the phenomenology or symptom profiles of childhood/adolescent depression with that of adult depression, evidence suggests that there may be heterogeneity between childhood/adolescent and adult depression, and also between depression in childhood and adolescence. This evidence comes from epidemiological studies that compare risk factors for childhood/adolescent and adult depression, as well as from studies examining rates of familial aggregation and continuity of childhood and adolescent depression.

One epidemiological study used a prospective design and showed that risk factors for depression in young people differ from those for depression in adult life [10]. Jaffee and colleagues assessed a range of putative risk factors for depression in childhood (occurring prior to the age of 9 years) [10]. The cohort was then assessed for MDD on six occasions between childhood and adulthood. The authors were therefore able to compare four groups of individuals: (1) those with no MDD; (2) those with MDD in childhood/adolescence only; (3) those with MDD in childhood/adolescence that recurred in adult life; and (4) those with MDD in adult life only. Individuals with an onset of depression in adulthood had a similar risk profile to those without a history of depression, with the exception of higher rates of sexual abuse (which was the only risk factor assessed retrospectively in adulthood). In contrast, individuals with depressive episodes in childhood/adolescence showed elevated rates of a range of childhood risk factors, including perinatal insults, parental psychopathology, motor skill deficits and caretaker instability. Therefore, this finding points to the likelihood of etiological heterogeneity between childhood/adolescent and adult depression. This requires further investigation in additional studies using prospective designs.

Long-term clinical follow-up studies and epidemiological studies show that there is strong homotypic continuity between adolescent and adult depression. Thus, both adolescent depressive symptoms and disorder predict episodes of depression in adult life [11-13]. Evidence of the continuity of childhood depression with adult depression is not as strong, and two independent follow-up studies of clinic-referred prepubertal depressed patients report low rates of homotypic continuity with depression in adulthood [14,15], and instead report heterotypic continuity where childhood depression cases show increased rates of other problems in adult life, including conduct disorder. Thus, prepubertal depression differs from postpubertal depression in terms of continuity with adult MDD. A prospective community study has reported that recurrence in early adult life could be a marker for etiological heterogeneity in childhood/adolescent depression [10]. That study found that childhood/adolescent MDD that did not recur in early adult life was characterized by a male preponderance and comorbidity with externalizing disorders, whereas childhood/adolescent MDD with recurrence in early adult life was characterized by a female preponderance and comorbidity with anxiety disorders [10]. This issue of etiological heterogeneity between childhood and adolescent depression has also been examined by family studies, as reviewed below.

Genetic factors associated with childhood and adolescent depression

Family studies

Family studies cannot disentangle similarity that is due to genetic factors from that due to environmental factors. However, they are an important first step in genetic epidemiology studies as they provide an upper limit to heritability estimates. They also provide information about the conditions under which familial aggregation is greatest, and this is useful for genomic studies. Family studies of MDD in young people have used two approaches: 'bottom-up studies' examining the relatives of depressed children/adolescents, and 'top-down studies' focused on the offspring of depressed parents. All studies have patterns of strength and weakness; however, it is worth noting that these may differ for bottom-up and top-down studies. In particular, clinical referral biases may be important to consider in bottom-up studies, as very high proportions of depressed children/adolescents never present at clinic [16], while top-down studies may show higher rates of aggregation than bottom-up studies given that depression in a parent adversely affects the family environment [17]. Studies of children/adolescents with MDD generally report a twofold increase in risk to first-degree relatives compared with healthy control groups. The offspring of depressed parents show a three- to fourfold increase in risk for MDD compared with the offspring of healthy control groups [18]. The prognosis of depression (if it develops) may also be particularly poor in these high-risk offspring [19].

One issue pertinent to genetic studies of depression has arisen from family studies using retrospective methods to date the onset of the disorder. Several such family studies report that MDD with an onset in early adult life (onset before age 20 or 30 years) shows higher levels of familial aggregation than depression with a later onset [20,21]. This finding has been extrapolated, and it has led some researchers to suggest that childhood-onset MDD cases should be the focus of molecular genetic studies [22]. However, it is important to bear in mind that familial

loading can be due to both genetic and environmental factors. Moreover, this pattern of results has not been confirmed in studies using prospective measures and those examining familial aggregation of childhood and adolescent onset MDD. Methodological issues relating to retrospective recall mean that prospective methods are preferable for assessing the timing of onset of depressive episodes [23,24]. Indeed, the only study that has directly compared the familiality of prepubertal, postpubertal and adult-onset depression found remarkably little difference among the rates of familial aggregation of depression [25], and the pattern of results suggested that prepubertal depression was slightly less familial than either adolescent or adult-onset depression. Furthermore, the two studies that have examined the continuity of prepubertal and postpubertal depression with depression in adult life both report low rates of homotypic continuity of childhood MDD compared with adolescent MDD with depression in adult life [14,15]; this highlights potential differences between childhood and both adolescent and adult depression. Weissman and colleagues [15,26] have suggested that there may be subdivisions within childhood-onset MDD; specifically, that there is a subtype of familial recurrent childhood MDD. However, given that so few family studies have distinguished between childhood- and adolescent-onset MDD, and that retrospective and prospective family studies report different results, this requires investigation in prospective studies that examine recurrence and continuity. Results of the studies suggesting differences between childhood/adolescent depression that occurs only in early life and that which recurs in adult life [10,26] have an important implication for molecular genetic studies of MDD: namely, that if recurrence does index a form of childhood MDD that is familial, genetic studies using a 'follow-back' approach that includes depressed adults who retrospectively report that their first onset was in childhood/adolescence (that is, those with early-onset MDD that recurs in adult life) will not necessarily yield the same results as genetic studies that include childhood/adolescent depressed probands [26].

Twin studies

Twin studies of children and adolescents have been used to examine the extent to which variation in depressive symptoms are due to genetic or environmental factors. A range of approaches looking at adopted children or children of twins have been used to assess the relative impact of genes and environment to transmission within families. In the classic twin design, which includes pairs of identical (monozygotic) and fraternal (dizygotic) twins reared together, the heritability estimate refers to the proportion of variation in a phenotype that is attributable to genetic factors. The fact that monozygotic twins share all their genes in common and, on average, dizygotic twins share 50% of their genes in common provides a 'natural experiment' that allows the heritability estimate to be statistically inferred and the remaining proportions of variation are attributed to environmental influences. Environmental influences are usually subdivided into shared environmental (that is, influences that tend to make twin pairs more similar) and non-shared or unique (that is, influences that impinge uniquely on one twin and tend to make twin pairs dissimilar). The heritability estimate is a statistic that includes the effect of all genes, as well as indirect genetic influences such as gene-environment correlation and gene-environment interaction. Twin studies of depressive symptoms in children and adolescents have shown that depressive symptoms in young people are heritable. However, there is marked variation in heritability estimates across different studies [18,27]. Some variability is expected because heritability estimates are population-based statistics; however, the magnitude of heritability estimates appears to differ according to who reports on the symptoms of the child (child, parent, teacher), meaning that firm conclusions are difficult to establish. This issue requires further investigation as it has implications for refining the phenotype for molecular genetic studies. One consistent finding from twin studies is that the influence of genetic factors on depression is small and non-significant in childhood and increases in adolescence [28-31]. One twin study reports that this age-related difference in genetic etiology of depression between childhood and adolescence may be partly due to gene-environment correlation, which increases around adolescence as young people have greater independence in selecting and shaping environments at this time [32]. Longitudinal studies also report that 'new' genetic influences emerge in adolescence [31], although no longitudinal study has specifically focused on the childhood-to-adolescence transition. There has been only one twin study of adolescent depressive disorder (in females aged 12 to 23 years, mean age at assessment 15 years) [23], and this reported a heritability estimate of 40% (95% confidence interval, 24 to 55), which is consistent with results from a meta-analysis of adult twin studies that reported a heritability estimate of 37% (95% confidence interval, 31 to 42) for MDD [33]. Thus, evidence to date suggests that genetic influences on risk for adolescent major depression are moderate, and account for around 40% of the phenotypic variation; for symptoms the figure is between 30% and 50%, but for depressive symptoms in childhood the figure is much smaller and non-significant [18]. One final group of relevant findings from twin studies are those from studies examining the etiology of high levels of depressive symptoms in children and adolescents (instead of depressive disorder). Here, the evidence is

highly consistent and shows that these are less heritable than depressive symptoms within the normal range. This surprising finding was evaluated by Glowinski and colleagues [23] when they compared heritability estimates for a broad phenotype of sadness and/or anhedonia lasting 2 weeks with that of a diagnosis of MDD. They found that the broader phenotype was largely influenced by shared environmental influences, whereas a diagnosis of MDD depended on both heritable and environmental factors. This illustrates the importance of precision in diagnostic definitions for molecular genetic studies: for instance, on the basis of current evidence, it would seem inappropriate to focus gene-finding studies on adolescents with high levels of symptoms.

Adoption studies

There have been three adoption studies that have examined depression-related phenotypes in children and adolescents (two examined internalizing problems (depression, anxiety and withdrawal) and one examined MDD) [34-36]. Interestingly, all of the adoption studies have found little evidence for genetic transmission of risk for depression. The most recent study by Tully and colleagues [36] examined similarity between adoptive (unrelated) parents and adolescents for lifetime MDD, as well as a control sample of non-adopted children and their biological parents. Adoptive adolescents whose unrelated parents had experienced lifetime MDD showed elevated rates of depression compared with adopted children whose unrelated parents had not had MDD (odds ratio, 2.19). That pattern of results is consistent with an important shared environmental component to the intergenerational transmission of depression. Inherited influences did make some contribution, as the same comparison in the biologically related group resulted in a slightly, though not significantly, higher risk (odds ratio, 2.96). Ongoing research is examining genetic and environmental contributions to the parent-child transmission of depression using alternative research designs, such as the children of twins design [37] and an *in vitro* fertilization design [38], and reports evidence consistent with environmental transmission of depression between parents and children [39].

Molecular genetic studies of childhood/adolescent depression

Molecular genetic studies of childhood/adolescent depression are in their infancy and have tended to be guided by results from studies of adult depression. These studies have tended to use a candidate gene approach and focus on functional polymorphisms in genes involved in pathways thought to be important in depression, including stress response and hypothalamic-pituitary-adrenal axis functioning. There are a small number of genetic-association studies of childhood/adolescent MDD that rely on small sample sizes. A number of studies have examined putative gene-environment interactions with childhood/adolescent MDD, where genes influence outcome by modulating response to environmental risk [40]. Pharmacogenetic studies of adolescent depression have recently begun, following reports of genetic variation influencing treatment responses to antidepressants in adults [41].

Some studies of childhood/adolescent depressive symptoms and MDD have focused on a variable nucleotide tandem repeat in the serotonin transporter gene. The serotonin transporter removes serotonin released into the synaptic cleft and is a key regulator of serotonergic neurotransmission. A repeat-length polymorphism in the promoter of this gene has been shown to affect the rate of serotonin uptake, with the short variant reducing serotonin transporter expression, resulting in higher concentrations of serotonin in the synaptic cleft compared with the long variant [42]. However, it should be borne in mind that there are low- and high-functioning forms of the long variant, meaning that the polymorphism is functionally tri-allelic [43]. In adults, the short variant has been associated with neuroticism and anxiety-related traits [42], an elevated cortisol response to stress [44], greater amygdala activity when viewing fearful emotional faces [45] and with depression when in combination with life stress [46]. Converging evidence from various sources therefore suggests that this polymorphism may be involved in reactivity to stress, although there are also non-replications [47-49]. In children/adolescents, one small study has reported significant association between the short variant and depression using a case-control design and a family-based association design [50]. However, the short variant has also been associated with childhood aggression as opposed to depression [51]. There are a number of gene-environment interaction studies where the effect of the short variant in combination with stress has been examined. One study reported that the short variant was associated with high levels of depressive symptoms in female adolescents in combination with life stressors [52], although there has been a non-replication in a large sample of prepubertal children using a measure of emotional problems [53]. Other studies have examined different measures of life stress and reported that the short variant modifies the effect of stress on depression symptom scores in adolescents [54]. Moreover, there have been reports of gene-by-gene-by-environment interactions with childhood maltreatment as the environmental factor [55]. Specifically, an interaction between the short variant of the serotonin transporter and the Val66Met polymorphism in the gene encoding brain-derived neurotrophic factor has been reported to be associated

with childhood depression in a group of maltreated children, but not in a healthy control group [55]. Goodyer and colleagues [56] examined the relationship between the serotonin transporter polymorphism, cortisol response and MDD in a 12-month follow-up study of 400 adolescents selected for high levels of adversity. The authors showed that possession of the short variant was associated with higher morning cortisol levels and that the combination of higher cortisol levels and the short variant predicted an episode of depressive disorder at 12-month follow-up in both males and females.

Finally, two small pharmacogenetic studies have reported genetic influences on poor treatment outcome in adolescent depression [57,58]. The first study reported lower efficacy of citalopram and higher suicidality scores for adolescents homozygous for the short variant of the serotonin transporter gene [57]. The second study examined antidepressant response in adolescents unresponsive to a selective serotonin reuptake inhibitor, and reported that genotypes in *FKBP5*, a gene that encodes a protein causing subsensitivity of the glucocorticoid receptor, are associated with suicidal events and behaviour [58,59].

Conclusions

Molecular genetic studies of childhood and adolescent depression are only just beginning and tend to include small samples. There are complex issues regarding phenotypic definition and heterogeneity that need to be addressed before molecular genetic studies begin in earnest. Longitudinal studies of community and high-risk groups will help to establish which definitions of childhood/adolescent depression yield the highest rates of familial aggregation, although it is clear that there are substantial environmental influences on depression in young people, particularly when intergenerational transmission between parents and children is examined. As well as influencing biological processes, genetic influences on depression may be indirect and affect disorder through influences on behaviour (gene-environment correlation) and susceptibility to environmental risk (gene-environment interaction). Research examining cognitive-affective processing - for instance, through functional brain imaging and neurocognitive approaches - may be useful in elucidating the complex pathways from risk factor (genetic or environmental) to disorder. Observations from genetic epidemiology show that particular definitions of depression in childhood/adolescence (childhood symptoms, high levels of symptoms in childhood and adolescence) are not significantly heritable and this means that genomic approaches are premature until further work has been done on refining phenotypic definitions for genetic studies.

Abbreviation

MDD, major depressive disorder.

Competing interests

The author declares that she has no competing interests.

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