Role of the serotonin transporter gene in susceptibility to mood disorders in children of depressed parents

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Objective
The aim of the study was to explore psychological and behavioral disturbances in a sample of Egyptian children with depressed parents and investigate the potential role of the short (s) alleles of the serotonin transporter-linked polymorphic region in developing depressive symptoms in both parents and their offspring.

Subjects and methods
The study included 20 families with depressed parents and their offspring (age 6–18 years), who were compared with 20 control families with healthy parents. The Child Behavior Check List was filled by parents for children to detect syndromal and subsyndromal symptoms of mood disorders and other psychiatric disorders in the offspring. Blood samples were drawn from all groups and PCR analysis was conducted to investigate the polymorphism of interest.

Results
The children of depressed parents scored higher than the children of control parents in almost all Child Behavior Check List internalizing and externalizing problem parameters. A significantly higher percentage of depressed parents (70%) were found to carry the risk allele (s) compared with control parents (35%) ($P = 0.03$). A similar, but nonsignificant, pattern of asymmetric allele distribution was also found among the offspring of the two groups (77.3 vs. 50%).

Conclusion
Parental depression must be recognized as a major risk factor of psychiatric morbidity in children. Greater emphasis should be placed on developing large-scale effective preventive interventions for families with parental depression.

Keywords:
children, depression, *5-HTTLPR*, parental, polymorphism

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Introduction

Depression is a disabling condition that adversely affects a person's social, academic, and occupational life. The most common age of onset is between 20 and 30 years, with a later peak between 30 and 40 years (Kessler *et al.*, 2003). In Egypt, around 2.7% of people suffer from major depression (Ghanem *et al.*, 2009). Children also suffer from depression, a condition that requires the attention of health services for prevention and treatment. As many as three in 100 young children and nine in 100 adolescents have serious depression (Park and Goodyer, 2000). Parental depression is among the strongest predictors of depression and other psychiatric disorders in offspring (Weissman *et al.*, 1987; Beardslee *et al.*, 1998; Warner *et al.*, 1999; Bureau *et al.*, 2009; Murray *et al.*, 2012). In general, children of depressed parents were estimated to be at a two- to four-fold risk of developing depressive disorders (Hammen *et al.*, 1990; Kramer *et al.*, 1998). Likewise, these children are at risk for other internalizing, and externalizing problems, in addition to academic and social failure (Lewinsohn *et al.*, 2003).

According to the report from the Institute of Medicine (England, 2009), at least 15 million children are living with a depressed parent in the USA. Moreover, the number of children exposed to parental depression is much larger when the entire span of childhood is considered, rather than a single year, and when other forms of parental mood disorders are included. Many parents who recover from an episode of depression continue to experience subclinical levels of depressive symptoms, with their children repeatedly exposed to associated disruptions in parenting (Brennan *et al.*, 2003).

In contrast, the elevated risk of psychopathology and functional impairment in the offspring of depressed parents does not prevent many of these children from functioning well over the life course without developing depression or other mental disorders (Lewandowski *et al.*, 2013; Lewandowski *et al.*, 2014). The term 'resilience' has been used to describe positive adaptation in the face of circumstances involving a high likelihood of maladjustment (Luthar *et al.*, 2006). In fact, it is the balance of risk factors and protective resources that determines outcome (Solantaus-Simula *et al.*, 2002a, 2002b).

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Over the past years, data have accumulated on several samples of depressed parents and their offspring. Weissman *et al.* (2005) followed a sample of offspring of depressed and nondepressed parents over 20 years, and all the offspring are now adults and have their own children. At the last assessment, rates of diagnosis of mood disorders and other disorders were three-fold in the now adult offspring compared with the comparison group (Weissman *et al.*, 2006). Lower maternal overprotection, greater offspring self-esteem, and higher intelligence quotient (IQ) were associated with greater odds of resilient outcome in the cohort (Lewandowski *et al.*, 2013).

An integrative model of the transmission of risk from depressed mother to child that incorporates biological and environmental factors was proposed (Goodman and Whitaker, 2002). The transmission of risk of depression from parent to child has been shown to be a bidirectional process. That is to say, although parental behaviors influence child outcome, the child's behavior likewise influences the parent. Similarly, Goodman and Gotlib's integrative model is strengthened by the bidirectionality inherent in its structure, in that the mechanisms for transmission of risk are proposed to overlap and interact with one another (Forbes *et al.*, 2008). Applying this model to the heritability of depression, a child who inherits a certain genetic makeup from a depressed parent has the raw materials for developing depressive symptoms, but only when certain environmental effects come into play does the combination of gene and environment create the end product – namely, a depressive disorder (Hammen *et al.*, 2010).

The serotonin transporter gene is known as the 'depression risk-gene'. It was reported that individuals carrying one or two short (s) alleles of the serotonin transporter-linked polymorphic region (*5-HTTLPR*) exhibit certain personality traits that predispose them to depression (Brown and Harris, 2008). In 2003, it was reported that s-carriers exhibit more depressive symptoms, full-blown depressive syndrome, and suicidal tendencies after exposure to stressful life events. Thus, this gene has become the most investigated genetic variant in psychiatry and also has been known as a mood-regulating gene (Hariri *et al.*, 2002; Brody *et al.*, 2009). Evidence for gene–environment interaction (G´E) involving the polymorphism in the promoter of the serotonin transporter genotype (*5-HTTLPR*) and adult depression was first reported using data from the Dunedin birth cohort (Caspi *et al.*, 2003). The short (s) less active allele was associated with a greater risk for adult depression in the presence of a history of either childhood maltreatment or multiple life events in a 5-year period before onset. The sl heterozygote showed intermediate predisposition between the ss and ll homozygotes. The finding is consistent with the research on the role of serotonin in animals and humans (Uher and McGuffin, 2008).

The current study aimed to study the differential rates of syndromal and subsyndromal symptoms of mood disorders in children of depressed parents in comparison with children of healthy controls. We also aimed to investigate the potential association between the short allele (s) of the serotonin transporter gene and the occurrence of depression in both parents and their offspring.

Subjects and methods

This paper is adapted from a thesis titled 'Role of Serotonin Transporter Gene in Susceptibility to Mood Disorders in Children and Adolescents of Depressed Parents', which was submitted by the last author to the Faculty of Medicine, Tanta University, as partial fulfillment of a Master's Degree in Neuropsychiatry. The study included the offspring of 20 families with depressed parents, recruited from both outpatient and inpatient sections of the department, who were compared with the offspring of 20 healthy control families. Control families were recruited from among those coming to the neurology clinic for minor neurological complaints (e.g. back pain, peripheral neuritis, etc). Parents were included if they had offspring between the ages of 6 and 18 years and accepted to participate in the study with a written consent. Parents were excluded if they suffered from mental retardation (IQ<70), schizophrenia, or schizoaffective or any mental disorders due to general medical conditions. Parents suffering from significant neurological conditions that could affect their collaboration with the study, such as multiple sclerosis or epilepsy, were also excluded. Families with depressed parents had the additional inclusion criterion of including at least one parent who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) lifetime diagnosis of major depressive disorder (MDD), whereas control families had the additional exclusion criterion of having a parent who met such a diagnosis. No exclusion for any psychiatric disorders was made in the offspring. Children with medical, neurological, or low IQ or with any condition that interfered with the interviews were not assessed face to face.

After acquiring informed consent, all patients were subjected to full psychiatric history and mental status examination, in addition to physical and neurological examination. The Fahmy and El-Sherbini scale (Fahmy and El-Sherbini, 1983) was used to collect demographic

and socioeconomic data. The Arabic version of Mini International Neuropsychiatric Interview 'M.I.N.I' was carried out to confirm the diagnosis of MDD in depressed parents and to exclude such a diagnosis in control parents (Sheehan *et al.*, 1998). This was translated and validated in Arabic (Ghanem *et al.*, 1999). The Child Behavior Check List (CBCL) was filled by parents for school-aged children to detect syndromal and subsyndromal symptoms of mood disorders or other psychiatric disorders in the offspring (El Defrawy *et al.*, 1995; Achenbach and Dumenci, 2001).

Blood samples were drawn from all groups (parents and offspring) after obtaining informed consent. DNA was extracted from 200 ml of frozen blood using the Qiagen Dneasy Kit (Qiagen, Hilden, Germany; Cat. #695061). Oligonucleotide primers flanking the *5-HTTLPR* and corresponding to the nucleotide positions −1416 to −1397 (stpr5, 5-GGC GTT GCC GCT CTG AAT GC) and -910 to -888 (stpr3, 5-GAC GGA CTG AGC TGG ACA ACC AC) of the *5-HTT* gene 5-flanking regulatory region were used to generate 484 or 528 bp fragments. PCR amplification was carried out in a final volume of 30 µl consisting of 50 ng of genomic DNA, 50 ng of each of sense and antisense primers, 15 µl of Taq PCR Master mix (Qiagen; Cat. #201445), 10% dimethyl sulfoxide, and 1 mol/l betaine. Annealing was carried out at 61 °C for 30 s, extension at 71 °C for 1 min, and denaturation at 95 °C for 30 s for a total of 35 cycles. The PCR products were electrophoresed through 5% polyacrylamide gel (acrylamide /bis-acrylamide ratio 19 : 1) at 60 V for 60 min. A 100 bp marker was used to measure the PCR product size for the L and S alleles.

Statistical analysis of the present study was conducted using the mean, SD, and the χ^2-test, with SPSS V.18 (IBM corporation, Armonk, New York, USA). Fully informed consent was taken from the parents. Participants and the ethical committee of the faculty of Medicine in Tanta University, which approved the study, were informed of any unexpected risks that could accrue during the course of the research.

Results

Of the total sample of parents with depression (n = 20), 6 (30%) were male and 14 (70%) were female. The age of depressed parents ranged from 25 to 45 years with a mean of 32.7 and SD of 2.1 years. Regarding the control parents (n = 20), 5 (25%) were male and 15 (75%) were female. The age of control parents ranged from 30 to 60 years with a mean of 44.8 years and SD of 8 years. Comparison of the two groups showed that depressed parents were significantly younger than the controls (P = 0.001), but there were no significant differences between the two groups regarding sex or socioeconomic status as estimated by the Fahmy and El-Sherbini score (P = 0.2, 0.4) (Table 1 and Fig. 1).

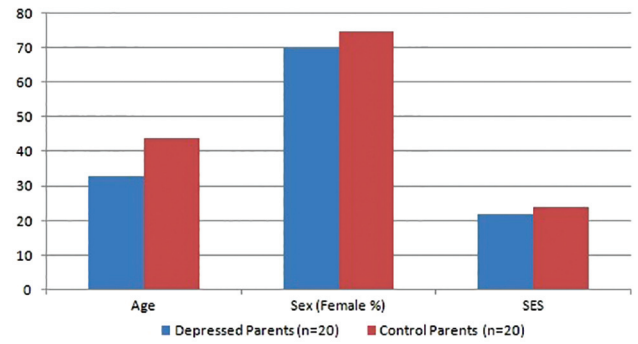
As regards offspring groups, the children of depressed parents (n = 22) were aged 10.6 years on average with an SD of 2.2 years. Twelve children were girls (54.5%) and 10 were boys (44.5%). The children of control parents were aged 9.4 years on average with an SD of 2.7 years. Most of those children were girls (85%, compared with 15% boys). Differences between the two groups did not reach statistical significance in any of the demographic variables ($P \geq 0.05$). The children of depressed parents showed less school, social, and total competence scores on CBCL ($P \leq 0.05$). Differences in participation in scholastic activities were not significant (P = 0.09) (Table 2 and Fig. 2).

Table 1 Comparison between depressed and control parents

Variables	Depressed parents (n = 20)	Control parents (n = 20)	Statistics	P-value
Age	32.7 ± 2.1	44.8 ± 8	t = 5.8	0.001
Sex (female, %)	70	75	χ^2 = 2.3	0.2
SES	21.8 ± 7.1	23.9 ± 7.9	t = 0.9	0.4

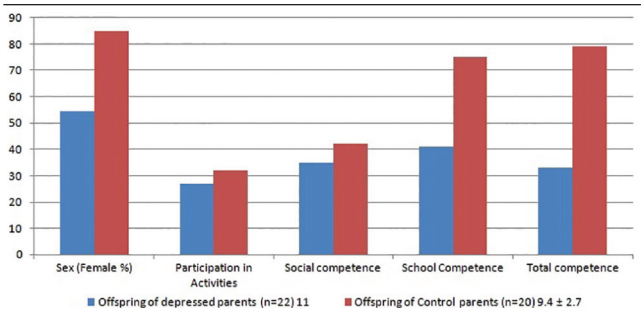
SES, socioeconomic status.

Figure 1



Comparison between depressed and control parents.

Figure 2



Differences between offspring of depressed parents and offspring of control parents (6–18 years old) regarding sociodemographic data and CBCL competence parameters. CBCL, Child Behavior Check List.

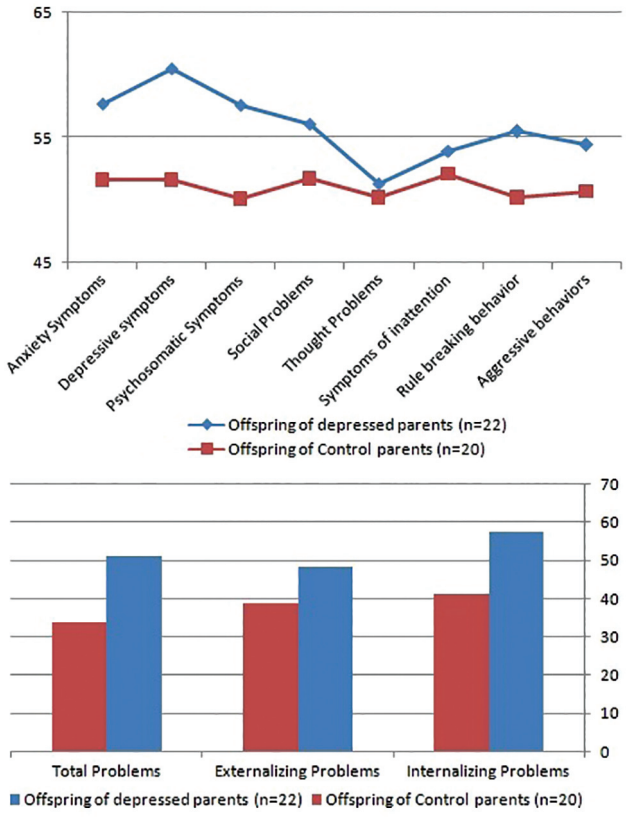
With the exception of thought problems and problems of inattention, the children of depressed parents scored higher than the children of control parents in all CBCL problem parameters. These include internalizing problems such as anxiety symptoms, depressive symptoms, psychosomatic symptoms, and social symptoms in addition to externalizing symptoms such as rule-breaking behavior and aggressive behavior (all $P \leq 0.05$). However, depressive and psychosomatic symptoms were characterized by highly significant differences ($P \leq 0.001$) (Table 3 and Fig. 3).

Table 2 Differences between offspring of depressed parents and offspring of control parents (6–18 years old) regarding sociodemographic data and CBCL competence parameters

CBCL subscale	Offspring of depressed parents (n = 22)	Offspring of control parents (n = 20)	Statistics	P-value
Age	10.6 ± 2.2	9.4 ± 2.7	t = 1.6	0.1
Sex (female, %)	54.5	85	χ^2 = 3.1	0.08
Participation in activities	27.01 ± 2.3	31.7 ± 4.2	t = 1.6	0.09
Social competence	34.5 ± 5.1	41.8 ± 11.5	t = 2.8	**0.03**
School competence	40.8 ± 5.3	74.5 ± 13.0	t = 0.3	**0.04**
Total competence	33.3 ± 8.5	79.1 ± 13.1	t = 0.3	**0.04**

CBCL, child behavior check list; P-value less than 0.05 is considered statistically significant (shown in bold).

Figure 3



Differences between offspring of depressed parents and offspring of control parents (6–18 years old) regarding CBCL problem parameters. CBCL, Child Behavior Check List.

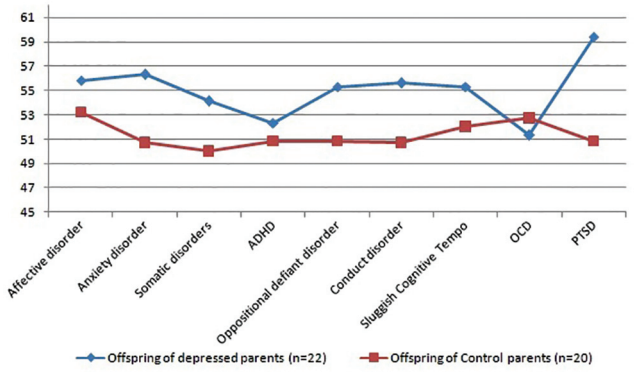
When CBCL DSM-oriented scales were explored, the above-mentioned differences in symptom scales were found to translate into corresponding psychiatric disorders. Internalizing problems manifested themselves in the form of affective disorders, anxiety disorders, somatic (somatoform) disorders, and post-traumatic stress disorders. In contrast, externalizing disorders were manifested in the form of oppositional disorder and conduct disorder. All P-values were significant (≤ 0.05), except those for somatic and post-traumatic disorders, which were highly significant (≤0.001). Notably, children of depressed parents scored higher than control children on sluggish cognitive tempo score despite the absence of a corresponding difference in attention score between the two groups (Table 4 and Fig. 4).

When the genotyping results of parent groups were compared, a higher percentage (70%) of depressed parents were found to carry the risk allele (s) compared with control parents (35%). The difference between the two groups was statistically significant (P = 0.03). A similar pattern of allele distribution was also found among the offspring of the two groups. Seventeen (77.3%) children of depressed parents carried the s allele as compared with 10 (50%) control offspring. However, the difference between the two offspring groups approached but did not reach the level of statistical significance (P = 0.07) (Table 5 and Fig. 5).

Discussion

We report higher internalizing and externalizing behavioral problems, in addition to lower levels of scholastic and social competence, in children of depressed parents. Internalizing problems, which took the form

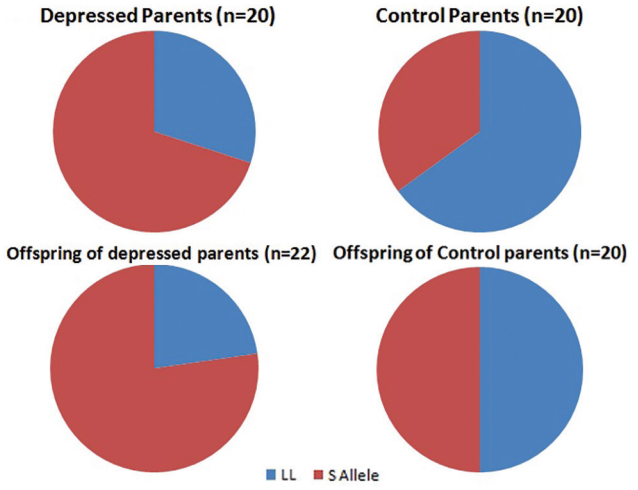
Figure 4



Differences between offspring of depressed parents and offspring of control parents (6–18 years old) regarding CBCL DSM-oriented disorders. CBCL, Child Behavior Check List; DSM, *Diagnostic and Statistical Manual of Mental Disorders.*

of depressive and psychosomatic symptoms, were more prominent than externalizing ones. The main psychometric tool utilized in this study was the CBCL, a cost-efficient and time-efficient screening instrument for a dimensional assessment of competences as well as behavioral and emotional problems in offspring at high risk for psychopathology (Biederman *et al.*, 1993, 2001, 2005; Faraone *et al.*, 2005). We also report that both depressed parents and their children were more likely to be carrying one or two short (s) alleles of the *5-HTTLPR* despite the fact that the difference in the offspring group did not reach the level of statistical significance.

Figure 5



Genetic distribution among parent and offspring groups.

To our knowledge, this is the first Arab and Egyptian study on the impact of parental depression on the mental and behavioral well-being of the offspring. Our results replicate and support previously reported results, which state that children of depressed parents are especially at risk for the development of various psychiatric and behavioral disturbances (Warner *et al.*, 1999; Weissman *et al.*, 2005; Pilowsky *et al.*, 2006; Bruder-Costello *et al.*, 2007). In a survey on a large number of mothers (n = 1357), adolescents whose mothers showed chronic, elevated, and stable subclinical latent depressive symptoms reported more internalizing and externalizing problems and acknowledged engaging in more risky behavior than did children of never depressed mothers (Campbell *et al.*, 2009).

Table 3 Differences between offspring of depressed parents and offspring of control parents (6–18 years old) regarding CBCL problem parameters

CBCL subscale	Offspring of depressed parents (n = 22)	Offspring of control parents (n = 20)	Statistics	P-value
Anxiety symptoms	57.7 ± 5.8	51.6 ± 3.4	t = 3.4	**0.03**
Depressive symptoms	60.5 ± 12.2	51.6 ± 2.5	t = 2.8	**0.009**
Psychosomatic symptoms	57.6 ± 7.6	50.1 ± 3.2	t = 2.0	**0.003**
Social problems	56.1 ± 5.3	51.7 ± 2.8	t = 2.5	**0.05**
Thought problems	51.3 ± 1.3	50.2 ± 0.4	t = 0.6	0.6
Symptoms of inattention	53.9 ± 5.1	52.1 ± 2.9	t = 1.2	0.3
Rule-breaking behavior	55.5 ± 6.03	50.2 ± 0.4	t = 3.2	**0.02**
Aggressive behaviors	54.4 ± 5.3	50.7 ± 1.1	t = 2.2	**0.04**
Internalizing problems	57.7 ± 10.9	41.3 ± 7.9	t = 11.4	**0.001**
Externalizing problems	48.3 ± 12.4	38.8 ± 7.5	t = 4.5	**0.006**
Total problems	51.2 ± 10.9	33.8 ± 11.2	t = 10.5	**0.001**

CBCL, child behavior check list; P-value less than 0.05 is considered statistically significant (shown in bold).

Table 4 Differences between offspring of depressed parents and offspring of control parents (6–18 years old) regarding CBCL DSM-oriented disorders

CBCL subscale	Offspring of depressed parents (n = 22)	Offspring of control parents (n = 20)	Statistics	P-value
Affective disorder	55.8 ± 8.0	53.2 ± 5.1	t = 1.7	**0.09**
Anxiety disorder	56.3 ± 6.4	50.7 ± 0.5	t = 1.6	**0.04**
Somatic disorders	54.1 ± 5.5	50.0 ± 0.4	t = 3.6	**0.009**
ADHD	52.3 ± 3.2	50.8 ± 1.2	t = 0.6	0.3
Oppositional defiant disorder	55.3 ± 6.2	50.8 ± 1.9	t = 3.3	**0.03**
Conduct disorder	55.6 ± 6.1	50.7 ± 1.5	t = 3.9	**0.02**
Sluggish cognitive tempo	55.3 ± 7.9	52.0 ± 2.9	t = 1.3	**0.09**
OCD	51.3 ± 1.7	52.7 ± 5.2	t = 0.2	0.5
PTSD	59.4 ± 5.15	50.8 ± 1.5	t = 3.9	**0.008**

ADHD, attention deficit hyperactivity disorder; CBCL, child behavior check list; DSM, *diagnostic and statistical manual of mental disorders*; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder; P-value less than 0.05 is considered statistically significant (shown in bold).

Table 5 Genetic distribution among parent and offspring groups

Genotype	Depressed parents (n = 20) [n (%)]	Control parents (n = 20) [n (%)]	Statistics	P-value
LL	6 (30)	13 (65)	χ^2 = 4.9	0.03
S Allele	14 (70)	7 (35)		
Genotype	Offspring of depressed parents (n = 22) [n (%)]	Offspring of control parents (n = 20) [n (%)]	Statistics	P-value
LL	5 (22.7)	10 (50)	χ^2 = 3.4	0.07
S Allele	17 (77.3)	10 (50)		

LL, homozygote; S allele, homozygote (SS) or heterozygote (SL).

Compared with their male counterparts, female individuals have been found to be more vulnerable to depressive disorders from adolescence through adulthood (England, 2009; Reeb *et al.*, 2010). However, many of the studies looking at the effects of maternal depression on offspring outcomes, in addition to the current study, have failed to consider the role of offspring gender (Sheeber *et al.*, 2002). Twin and adoption studies have established that genetics explain ~30–40% of the variance in adult MDD. Family studies have found significantly higher risks for depression among the offspring of depressed parents (Rice *et al.*, 2002). In agreement with our results, several previous studies reported evidence for the association of the S allele and S/S genotype with MDD, unipolar or bipolar depression, and also significant association of the S allele with seasonal affective disorder (Collier *et al.*, 1996a, 1996b; Gutierrez *et al.*, 1998; Rosenthal *et al.*, 1998). Lesch *et al.* (1996) and Lesch and Mossner (1998) also reported the influence of *5-HTTLPR* on the expression of *5-HTT*. They found the short variant of *5-HTTLPR* to reduce transcriptional activity of the gene promoter *in vitro* and to be associated with depression-related personality traits.

Over the past years there has been considerable progress in delineating the gene-by-environment interplay in determining the range of outcomes in children. In addition, progress has been made in identifying the risk mechanisms and moderators that underlie the transmission of disorder and in developing effective prevention programs (Beardslee *et al.*, 2011). Molecular genetics has focused on finding specific genes that may affect outcomes. Our genetic results agree with the conclusion made by Caspi *et al.* (2003), who stated that individuals with one or two copies of the short allele of the *5-HTT* promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events compared with individuals homozygous for the long allele. Other studies (Karg *et al.*, 2011) have shown that the s allele of the *5-HTTLPR* polymorphism confers increased risk of depression in conjunction with negative life events. In addition, a recent study (Starr *et al.*, 2012) suggested that the association between stress, depression, and the *5-HTTLPR* genotype may be bidirectional, as the short allele may contribute to stress generation in addition to stress reactivity. Less evident difference between the offspring groups in the current study may reflect the need for genetic and environmental factors in this group for full-blown depressive syndrome to be evident in the offspring.

Father–child conflict has been found to mediate the contribution of paternal depression to the offspring's internalizing and externalizing symptoms (Kane and G, 2009). Parental disengagement, responsiveness, unpredictability, expressed emotion, and hostility have been found to affect the offspring in the context of parental depression (Lovejoy *et al.*, 2000; Frye and Garber, 2005; Feng *et al.*, 2007; Dietz *et al.*, 2008) as has parent–child conflict (Kane and G, 2009). Increased chronicity and severity of parental depression have long been shown to increase the likelihood that children will become ill (Brennan *et al.*, 2000, 2003; Campbell *et al.*, 2009). In contrast, lower maternal overprotection, greater offspring self-esteem, and higher IQ were associated with greater odds of resilient outcome defined by consistently high functioning (Lewandowski *et al.*, 2014.

Despite this evidence of the involvement of the short variant in the etiology of depressive symptomatology, association studies of patients with MDD and control subjects have yielded conflicting results (Furlong *et al.*, 1998; Serretti *et al.*, 2002; Anguelova *et al.*, 2003; Mendlewicz *et al.*, 2004). The overall result of a recently published large meta-analysis comprising 941 patients with MDD and 2110 control subjects was negative (Anguelova *et al.*, 2003). Another meta-analysis also yielded no evidence that the serotonin transporter genotype, alone or in interaction with stressful life events, is associated with an elevated risk of depression (Risch *et al.*, 2009). This discrepancy in results might be due to a variety of factors, including ethnicity and sample size.

Currently, the problem of youth depression is both significant and under-recognized. The costs of treatment are high, and most children do not receive treatment. Parental depression must be recognized as a major public health problem. Much greater emphasis on developing large-scale effective preventive interventions for families

with parental depression is needed (NRCaIoMP, 2009). Moreover, prevention efforts should be integrated into primary care and school systems. Prevention offers one of the best ways of addressing health disparities, another key public health concern.

Finally, it is important to highlight the limitations of this study. First, the small size of the sample might limit the generalization of the results on Egyptian children or children with depressed parents in general. This small number did not allow the differential evaluation of psychiatric and behavioral problems in different age categories of children – for example school-aged children versus adolescents. Second, the information collected in this study was obtained only from parent reports; no teacher reports were obtained as most of the families were interviewed on only one occasion. Thus, inaccurate reporting due to parents' underestimation or overestimation of the symptoms might have occurred. Third, subjects were not formally evaluated through a structured or semistructured interview. The high validity and reliability of the well-known tool CBCL might decrease but does not suffice to replace a formal psychiatric interview. The validity of CBCL in diagnosing psychiatric disorders was questioned, especially in chronically ill children. Furthermore, other confounding factors, such as family conflicts, parenting styles, and medications received by children, were not taken into account.

Conclusion

Children with depressed parents suffer from high internalizing and externalizing problems. These internalizing problems tend to present in the form of depressive and psychosomatic symptoms, whereas externalizing problems tend to appear in the form of oppositional and conduct problems. The S allele of the *5-HTTLPR* polymorphism was found to be disproportionately represented in both depressed parents, and to a lesser extent in their offspring. More effort needs to be exerted for the early identification and management of psychological morbidity in children with depressed parents.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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