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SPECIAL ISSUE

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Finding gene-environment interactions for generalised anxiety disorder

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Abstract It is becoming increasingly apparent that genetic research into psychiatric disorders would benefit from consideration of the environment because these risk mechanisms are likely to interact. Despite generalised anxiety disorder (GAD) being one of the most prevalent disorders presented in primary care, there is a paucity of published studies of gene-environment interactions (G × E) for this phenotype. This article describes how our current knowledge of GAD is useful in designing studies of G × E for GAD. To increase the chances of identifying replicable G × E for GAD further information is needed with regards to: defining and measuring GAD, difficulties co-occurring with GAD, quantitative genetic estimations for GAD, specific genes associated with GAD, and specific environmental risks for GAD.

Key words generalized anxiety disorder · anxiety · genes · environment

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Introduction

An eminent geneticist recently gave a talk on psychiatric genetics. He ended his talk by concluding that there is little point searching for genes for a disorder without simultaneously considering environmental influences. While this view could be considered somewhat extreme, the importance of exploring interactions between genes and the environment is increasingly evident. In spite of this, there is a dearth of research reporting gene-environment interactions in relation to many common psychiatric disorders including generalised anxiety disorder (GAD). GAD is characterised by persistent chronic worry and tension, often including symptoms such as sleep difficulties, lack of concentration and restlessness (Diagnostic and Statistical Manual, DSM-IV, [1]). This disorder is one of the most prevalent mental disorders seen in primary care. For example, a recent review paper estimated the 12-month prevalence of GAD to be about 2% for adults in Europe [41] and results from the National Comorbidity Survey found the lifetime prevalence of GAD to be 5% [36]. Furthermore, the lifetime prevalence GAD using a broader definition (whereby the stipulation of 6 months duration is relaxed to a single month) has been estimated at 12% for males and 18% for females [29]. This article addresses issues that need to be considered on the way to discovering replicable gene-environment interactions for GAD. The specific ideas developed here are partly based on more general strategies for investigating interactions between measured genes and environments proposed by Moffitt et al. [46].

Gene-environment interactions

Gene-environment interaction (G × E) refers to genetic sensitivity or susceptibility to environmental experience. To illustrate this point, carriers of a certain "risk" allele (version of a gene) could be more likely to become anxious following a stressful life event as compared to carriers of another "non-risk" allele. Although most genetic research is conducted without consideration of the environment (and conversely the majority of environmental research is conducted without regards to genes), it is clear that interdisciplinary research assessing both types of influence may prove fruitful. For example, if an allele is more likely to be associated with a trait following conditions of environmental stress, the gene–trait association may be buried in a study populated by individuals who have experienced mixed levels of stress. Similarly, an environmental influence may appear weak in a sample diverse for a specific gene, yet may be much greater in individuals with a specific "risk" version of that gene. To further understanding of both genetic and environmental influences on various traits there has recently been a marked interest concerning G × E research. However, only a handful of published studies to date have focused on generalised anxiety. One such study led by Silberg demonstrated that genetic variance for anxiety increased from 19% in adolescent girls who had not experienced adverse life events, to 44% in those who had two such experiences ([58], see also [11]). A further study demonstrated an interaction between a measured genetic variable (the short 5-HTT allele) and an environmental variable (low social support) in predicting phenotypes associated with GAD in children (observed behavioural inhibition and mother-reported shyness) [18]. It is hoped that the current article will stimulate further research into this area and such information will help to elucidate the pathways by which genes influence GAD and may eventually be useful in developing preventive programmes and treatments for this common disorder.

GAD

Measurement

As with any type of study, it is essential to precisely define and measure the phenotype. GAD can be considered in terms of symptoms (e.g. see the Penn State Worry Questionnaire, 45) or as a disorder [54] and measured using self-reports or clinical interviews. In order to provide robust evidence of a G × E, it is important to assess GAD in a variety of ways (e.g. using different measures, informants and occasions). Indeed, some of the most widely cited reports of G × E have measured the outcome variable in multiple ways [6, 8]. For example, one study explored the association between childhood maltreatment and a genotype associated with varying levels of monoamine oxidase (a key enzyme involved in the degradation of neurotransmitters including serotonin and dopamine) in association with later antisocial behaviour. Antisocial behaviour was measured as a conduct disorder in standardised assessments according to DSM-IV criteria; by self- and informant-reports of behaviour; and in terms of convictions [6]. In addition to allowing internal replications of results, multiple reports enable the calculation of error-reduced composites, which increase the likelihood of detecting genetic and genuine environmental effects.

A complementary approach to measuring GAD is to examine endophenotypes for this disorder. Endophenotypes are intermediate phenotypes that are more proximal to the genes influencing a disorder than its signs and symptoms [21]. Endophenotypes are conceptualised as risk markers of a disorder and may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological. Focusing on endophenotypes has certain advantages over studying GAD directly, such as providing greater statistical power to identify genes (due to endophenotypes having greater proximity to genes than signs and symptoms of GAD) and providing cues as to the pathways by which genes influence GAD. Indeed, it has been suggested that G × E and neuroscience research must come together to benefit both fields [7]. A number of studies have explored neural structures relevant to the pathophysiology of generalised anxiety disorder, showing atypical responses in the amygdala and ventral prefrontal cortex in anxious individuals as compared to controls (e.g. 44, 48, 61). Further studies have found associations between certain brain responses and genes, both of which have been independently linked to anxiety. For example, research shows that the short allele of the 5-HTT promoter polymorphism is associated with greater neuronal activity in the amygdala in response to fearful stimuli ([26], see also [4, 19, 25, 27]). As the amygdala is involved in the detection of environmental threat and its reactivity is genetically moderated, it is likely that this brain structure is a good focus point for future G × E research.

Comorbidity

Although GAD sometimes occurs alone, it commonly co-occurs with other difficulties including other anxiety disorders (e.g. social phobia, specific phobia and panic disorder), as well as other types of difficulties including chronic fatigue syndrome and chest pain (for a review, see [49]). The association between GAD and major depressive disorder (MDD) has received particular attention as research has demonstrated high levels

of comorbidity between these disorders (GAD correlates more highly with MDD than with other disorders, 37). With regards to concurrent comorbidity, results from the US National Comorbidity Survey revealed that 17% of the respondents with lifetime MDD had also experienced GAD [38]. Research also suggests sequential bidirectional comorbidity between the two conditions with data from one prospective longitudinal study revealing anxiety preceded depression in 41% of cases and depression preceded anxiety in 36% of cases [47]. There are many possible ways of dealing with comorbidity in research, including focusing exclusively on "pure cases" which may increase power to detect effects by reducing noise. However, the fact that comorbidity represents an epidemiological reality suggests that it may be challenging to recruit adequate samples of "pure cases", and excluding comorbid cases may result in an artificial representation of factors associated with GAD in the general population. Instead, by measuring potentially co-occurring conditions, it is possible to statistically examine the influence of comorbidity on any association revealed.

Twin studies

Twin data can be used to estimate the magnitude of genetic and environmental influences on individual differences in a trait such as GAD in a population. This is achieved by comparing the similarity of identical twins (who are genetic clones of one another) and nonidentical twins (who share on average half of their segregating genes, i.e. those genes that make individuals differ from one another) (see [52] for further information). Such studies typically partition variance of a trait into additive genetic influences (genetic influences for which combined effects are equal to the sum of individual effects), shared environmental influences (those that make individuals within a family similar) and nonshared environmental influences (those that make individuals within a family differ).

There have been numerous quantitative genetic investigations of GAD with varying estimates of genetic, shared and nonshared environmental influences. A meta-analysis by a group of leading researchers at the Virginia Institute for Psychiatric and Behavioural Genetics estimated the heritability of GAD in adults to be .32, with small shared environmental influence for females but not males, and the rest of the variance attributable to nonshared environmental influences [28]. Finding that GAD is heritable has led researchers to pose further questions such as whether genetic influences increase with environmental risk exposure.

In addition to twin studies of GAD in adults, there are also twin studies of different types of anxiety in children and adolescents [12, 23]. Some of these studies suggest that there is smaller genetic influence and larger shared environmental influence in children as compared to adolescents (e.g. with regards to separation anxiety, see [15]) highlighting the possibility that genes that interact with the environment only emerge in adolescence. Similarly, environmental risks are also likely to dynamically unfold across development. Empirical tests of the hypothesis that age is an important moderator of G × E for GAD are therefore needed. Towards this goal, our own group cross-sectionally compared G × E results for different anxiety subtypes in two samples of twins at different ages [39]. We reported an increase in genetic effects across independent negative life events for separation anxiety in childhood and panic in adolescence.

As well as providing estimates of genetic, shared and non-shared environmental influences on GAD, quantitative genetic studies are also able to provide information about risk factors underlying co-occurring traits. For example, such models are able to estimate the extent to which genes influencing one disorder (e.g. GAD) are the same as those influencing another disorder (e.g. MDD). Similarly, the overlap between shared environmental factors influencing different disorders, as well as nonshared environmental factors influencing different disorders, can also be examined. Such information can be informative when planning G × E studies, as it may be useful for selecting candidate genes and environmental factors to explore. For example, strong genetic overlap between MDD and GAD suggests that genes known to influence MDD may be good candidates for exploration with regards to GAD (e.g. [35, 55]). Quantitative genetic research focusing on GAD and other difficulties (e.g. neuroticism, [29, 42]) may also be informative in stimulating hypotheses for future research by suggesting which genetic and environmental influences are likely to be important (based on previous research specifying genetic and environmental influences on each trait individually and knowledge about the overlap between influences on these phenotypes).

Perhaps more directly relevant to the issue of G × E, it is possible to examine whether estimated genetic influences interact with measured environmental influences on a trait using twin data [53]. These statistical G × Es have been found for a number of traits including anxiety [11, 58] and major depression, which commonly co-occurs with GAD [38]. Indeed, in a study by Kendler et al. [33], it was found that the likelihood of developing a major depression episode was greatest amongst individuals at genetic risk, if they also experienced a stressful life event. Such studies are useful in providing hypotheses for research, as the environmental measure (in this example, stressful life events), is an obvious candidate for inclusion in future interaction studies including measured genes (see [46]).

Genes

Obvious genes to test in interaction models are those, which have been associated with GAD previously.

Much of the work in this area has focused on serotonin genes, as serotonin is widely believed to be involved in the pathophysiology of anxiety disorders, and certain anxiolytic (anxiety relieving) drugs target the serotonin transporter. One study found that patients with GAD had a higher frequency of an allele containing 12 copies of the variable number tandem repeat in the second intron of the serotonin transporter gene as compared to controls [50]. An additional study reported an association between the short allele of the promoter region of the serotonin transporter and GAD [64]. Further reports have focused on monoamine oxidase A (MAO-A), which is an enzyme involved in the catabolism of neurotransmitters including serotonin and dopamine. One study found that >3 repeat alleles of the MAO-A gene polymorphism were greater in females suffering GAD as compared to controls [57]. The link between MAO-A and GAD has been emphasised elsewhere, with a reported association between the MAO-A 941T allele and GAD, although not panic disorder or major depression [60]. Although the results of this study suggest a segregation of GAD from major depression with regards to MAO-A T941G, the strong genetic overlap between MDD and GAD revealed by twin studies (e.g. [35, 55]) suggests that candidate genes involved in G × E for GAD may also come from studies focusing on MDD. For example, there is mounting evidence to suggest that individuals with one or two copies of the short allele of the promoter region of the serotonin transporter (5-HTT) gene are more likely to experience depression following environmental stress as compared to those with two long versions of the allele (e.g. [8, 14, 31, 34, 62]), although not all studies have reported this interaction (e.g. [20, 59]). Coupled with the finding that 5-HTT is associated with GAD, researchers have been led to investigate the possibility of an association between stressful life events and the 5-HTT gene in predicting general anxiety syndrome [34]. This study did not reveal a significant interaction, which is intriguing given the interactions between stressful life events and the 5-HTT gene in predicting episodes of major depression in the same sample. Discussing this finding, Rutter [56] suggests that although genes for anxiety and depression may be shared, genetic risk for anxiety and depression may operate through different mechanisms (perhaps genetic risks for anxiety do not interact with environmental risk factors, or interact with environmental risk factors not explored in this study). Studies exploring genes associated with depression have highlighted other candidate genes for further exploration including brain derived neurotrophic factor polymorphisms, which have been associated with bipolar disorder (for recent reviews of the genetics of depression and related traits, see [30, 40]). Twin studies have also suggested moderate to high genetic overlap between neuroticism and GAD [29, 42] suggesting that genetic polymorphisms that have been linked with neuroticism previously may be good candidates for further exploration.

When choosing between polymorphisms for investigation in studies, a practical consideration is the frequency with which the polymorphism occurs in the general population. In a moderately sized sample, associations with GAD are clearly more likely to be identified when focusing on commonly occurring (as compared to rarer) polymorphisms. Despite an array of candidate genes to test, previous G × E research suggests that certain genes associated with GAD may only be revealed once the environment is taken into consideration. Hence, genes, which have not yet been linked to a specific disorder, but have been shown to moderate environmental (e.g. stressor) responsiveness, may also be sensible candidates for further exploration. Studies illustrating these types of associations often involve animals, and one study of this kind demonstrated that length variation of the serotonin transporter gene-linked polymorphic region in rhesus monkeys interacts with early experience (having been raised by parents vs. having been raised by peers) to affect central serotonin functioning ([3], see also [2, 9]).

Environment

In addition to twin data providing information about environmental factors associated with GAD, non-genetic analyses have also been important. For example, a report focusing on the population-based Virginia Twin Registry examined life events associated with generalised anxiety and major depression [32]. Amongst interesting results, it was found that *danger events* (those associated with the anticipation of dire consequences) were associated with pure generalised anxiety but not pure major depression. Conversely, *humiliation events* (those associated with feeling devalued, rejected or having failed) were associated with pure major depression but not pure generalised anxiety. Generalised anxiety and major depression co-occurred and risk factors for pure major depression and pure generalised anxiety were both important for these co-morbid cases. Such findings are relevant to the selection of measured environment in G × E studies and confirm the importance of considering co-occurring conditions when designing a study, as environmental risk appears to vary depending on the treatment of comorbidity. This study also highlighted the importance of timing when considering environmental events. For example, *loss events* (those associated with a real or imagined loss of a person, possession, health, respect etc) were associated with pure generalised anxiety occurring in the same month but not occurring 1, 2 or 3 months subsequently. Life events involving danger or physical threats (i.e., to life or limb) as discussed earlier, are likely to be appropriate environmental factors to include in models of G × E in relation to GAD (see also 17). Indeed, it is

possible that including social threat environmental influences such as humiliation and public shame (as opposed to physical threat) in studies of G × E may make it difficult to identify true interactions. Physically threatening life events are particularly suitable environmental risks as they are proximal (i.e., specific factors directly affecting the individual). Other proximal risk factors for GAD include being widowed, separated or divorced [22, 63]. Distal risk factors such as being middle-aged or from a low-income bracket have also been associated with GAD [22, 63]. Distal risk factors are less appropriate for inclusion in G × E models as they may have their effects on GAD through proximal risk factors (see [46] for a more general discussion of this issue).

Although many of the studies exploring risk factors for GAD focus on adults, anxiety disorders often first appear early in life. For example, recently published data from the prospective Dunedin Multidisciplinary Health and Development Study of an entire birth cohort revealed that 38% of adults aged 32 years with GAD suffered anxiety disorders at ages 11–15 years [24]. This highlights the potential scope to examine G × E for GAD in young people as well as in adults which may be beneficial as understanding the mechanisms by which pediatric anxiety develops may be particularly important for developing preventions and treatments for these common difficulties. Although certain "environmental" factors may be relevant to both the child and adult samples (e.g. threatening life events have also been associated with anxiety in children, [13]), this is not always the case. For example, it would be absurd to examine ones own marital status in a study focusing on G × E for GAD in children, who are below the age of marital consent. In contrast, it would be more appropriate to include information about parenting (which has been associated with childhood anxiety, for a recent review, see [5]). Such risk factors can also be included in studies focusing on adult participants, although when obtaining retrospective reports, there may be inherent problems related to recall accuracy.

Although many of the risks considered thus far are often thought as "environmental" risks, it is clear that genes influence exposure to many of these "environmental" risks (a phenomenon known as gene-environment correlation, rGE). Indeed, a study of childhood depression found that there was a substantial genetic influence on the association between parental negativity and adolescent depression, which the authors interpreted as likely to result from an evocative gene-environment correlation, with adjustment problems influenced by genetic propensities evoking negative reactions from others [51]. It is important to control for rGE when searching for G × E due to a number of reasons. One such reason is that if twin studies reveal greater genetic effects for GAD at higher levels of environmental risk (e.g. when someone has experienced more threatening life events) this could suggest that environmental events impact on heritability (G × E) or people with "risky" genotypes are more likely (for reasons related to their genetic make-up) to be exposed to numerous environmental risks (rGE). Furthermore, associations between a measured risk genotype and environmental risk could reflect the measured risk genotype interacting with unmeasured genes, which are associated with the environmental risk (rGE) rather than a true interaction between the measured gene and the environment (G × E). There are various ways of controlling for rGE, and this is possible when examining interactions in twin and adoption samples.

What now?

To summarise, as with all genetic research it is fundamental to start with a clearly defined and well-measured phenotype. Indeed, refinement of definition and measurement of phenotypes is a continually evolving process and research which is currently underway to address the issues of how best to conceptualise GAD in the DSM-V may eventually be useful when designing studies of G × E (e.g. see [47]). It is also important to continue considering endophenotypes, as although research of this type is still in its infancy, combining G × E and endophenotype research holds great promise for a developed understanding of the pathways by which genes influence behaviours.

Although we now have information about specific genetic and environmental influences, which can be used to test hypotheses about G × E for GAD, it is clear that there is scope to further specify genetic and environmental influences. Indeed, it is apparent that multiple genes and environmental influences are likely to be associated with GAD, suggesting that the replicated genetic and environmental influences identified thus far represent the tip of the iceberg with regards to factors influencing GAD. Capitalising on improved research methods (e.g. microarrays, neuroimaging and single gene manipulations in animal models), different types of researches (e.g. MZ twin studies, prospective longitudinal epidemiology and experimental and animal research), and developed knowledge of associated phenotypes (e.g. MDD and neuroticism) holds great promise for the identification of further risk factors. Of note, the inclusion of more precise phenotypes and robust influences on these phenotypes will reduce the sample sizes necessary to detect effects in studies of G × E.

In addition to obtaining further specific information with regards to the conceptualisation of GAD as well as genetic and environmental influences, the time is ripe to start testing the models of G × E, and data and techniques available for such purposes are abundant. Given the excitement surrounding the G × E approach to understand the mechanisms underlying common difficulties, it is surprising that

there is very little research of this type addressing GAD. We believe that the greatest advances will be made in this field by collaborations between the very best scientists from different fields. Indeed, admirable efforts by psychologists with background knowledge of environmental risks for disorders but lacking genetic knowledge may result in limited studies of G × E. Similarly, geneticists lacking a rich understanding of issues related to environmental risk may find their G × E research disappointing. Together, researchers are likely to make groundbreaking contributions to the field of G × E for GAD. Indeed, geneticists are becoming increasingly interested in the role of epigenetics (heritable information distinct from the DNA sequence itself) on phenotypes [16]. Notably, research in this field has demonstrated that environments may impact on gene expression. Additionally, the epigenome is particularly susceptible to environmental influences during certain developmental periods [10]. This further emphasises the importance of bringing together researchers from different fields in order to advance the understanding of G × E for GAD still further.

Finally, psychiatric research is conducted with the eventual aim of alleviating suffering by preventing difficulties from developing and addressing those that do. It is therefore particularly salient that there has been a recent interest in genes as moderators of response to treatment for psychiatric disorders (e.g. depression, for a review see [43]). Although to date research of this type has not focused upon GAD, this type of G × E research is likely to be of key significance for clinicians and patients alike.

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References

1. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. American Psychiatric Association, Washington DC
2. Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML, Schwandt M, Champoux M, Lesch KP, Goldman D, Suomi SJ, Higley JD (2004) Rearing condition and rh5-HTTLPR interact to influence limbic–hypothalamic–pituitary–adrenal axis response to stress in infant macaques. Biol Psychiatry 55:733–738
3. Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, Champoux M, Suomi SJ, Linnoila MV, Higley JD (2002) Early experience and serotonin transporter gene variation interact to influence primate CNS function. Mol Psychiatry 7:118–122
4. Bertolino A, Arciero G, Rubino V, Latorre V, De Candia M, Mazzola V, Blasi G, Caforio G, Hariri A, Kolachana B, Nardini M, Weinberger DR, Scarabino T (2005) Variation of human amygdala response during threatening stimuli as a function of 5′HTTLPR genotype and personality style. Biol Psychiatry 57:1517–1525
5. Bogels SM, Brechman-Toussaint ML (2006) Family issues in child anxiety: attachment, family functioning, parental rearing and beliefs. Clin Psychol Rev 26:834–856
6. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002) Role of genotype in the cycle of violence in maltreated children. Science 297:851–854
7. Caspi A, Moffitt TE (2006) Opinion—gene-environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci 7:583–590
8. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389
9. Champoux M, Bennett A, Shannon C, Higley JD, Lesch KP, Suomi SJ (2002) Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates. Mol Psychiatry 7:1058–1063
10. Dolinoy DC, Weidman JR, Jirtle RL (2007) Epigenetic gene regulation: linking early developmental environment to adult disease. Reprod Toxicol 23:297–307
11. Eaves L, Silberg J, Erkanli A (2003) Resolving multiple epigenetic pathways to adolescent depression. J Child Psychol Psychiatry 44:1006–1014
12. Eley TC, Bolton D, O'Connor T. G., Perrin S, Smith P, Plomin R (2003) A twin study of anxiety-related behaviours in pre-school children. J Child Psychol Psychiatry 44:945–960
13. Eley TC, Stevenson J (2000) Specific life events and chronic experiences differentially associated with depression and anxiety in young twins. J Abnorm Child Psychol 28:383–394
14. Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, McGuffin P, Plomin R, Craig IW (2004) Gene-environment interaction analysis of serotonin system markers with adolescent depression. Mol Psychiatry 9:908–915
15. Feigon SA, Waldman ID, Levy F, Hay DA (2001) Genetic and environmental influences on separation anxiety disorder symptoms and their moderation by age and sex. Behav Genet 31:403–411
16. Feinberg AP (2007) Phenotypic plasticity and the epigenetics of human disease. Nature 447:433–440
17. Finlay-Jones R, Brown GW (1981) Types of stressful life events and the onset of anxiety and depressive disorders. Psychol Med 11:803–815
18. Fox NA, Nichols KE, Henderson HA, Rubin K, Schmidt L, Hamer D, Ernst M, Pine DS (2005) Evidence for a gene-environment interaction in predicting behavioral inhibition in middle childhood. Psychol Sci 16:921–926
19. Furmark T, Tillfors M, Garpenstrand H, Marteinsdottir I, Langstrom B, Oreland L, Fredrikson M (2004) Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. Neurosci Lett 362:189–192
20. Gillespie NA, Whitfield JB, Williams B, Heath AC, Martin NG (2005) The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. Psychol Med 35:101–111
21. Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160:636–645
22. Grant BF, Hasin DS, Stinson FS, Dawson DA, Ruan WJ, Goldstein RB, Smith SM, Saha TD, Huang BJ (2005) Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalised anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med 35:1747–1759
23. Gregory AM, Eley TC (2007) Genetic influences on anxiety in children: what we've learned and where we're heading. Clin Child Fam Psychol Rev 10:199–212
24. Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R (2007) Juvenile mental health histories of adults with anxiety disorders. Am J Psychiatry 164:301–308
25. Hariri AR, Drabant EM, Munoz KE, Kolachana LS, Mattay VS, Egan MF, Weinberger DR (2005) A susceptibility gene for affective disorders and the response of the human amygdala. Arch Gen Psychiatry 62:146–152

26. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR (2002) Serotonin transporter genetic variation and the response of the human amygdala. Science 297:400–403
27. Heinz A, Braus DF, Smolka MN, Wrase J, Puls I, Hermann D, Klein S, Grusser SM, Flor H, Schumann G, Mann K, Buchel C (2005) Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. Nat Neurosci 8:20–21
28. Hettema JM, Neale MC, Kendler KS (2001) A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 158:1568–1578
29. Hettema JM, Prescott CA, Kendler KS (2004) Genetic and environmental sources of covariation between generalised anxiety disorder and neuroticism. Am J Psychiatry 161:1581–1587
30. Huezo-Diaz P, Tandon K, Aitchison KJ (2005) The genetics of depression and related traits. Curr Psychiatry Rep 7:117–124
31. Kaufman J, Yang BZ, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH, Gelernter J (2004) Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci USA 101:17316–17321
32. Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA (2003) Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalised anxiety. Arch Gen Psychiatry 60:789–796
33. Kendler KS, Kessler RC, Walters EE, MacLean C J, Neale MC, Heath AC, Eaves LJ (1995) Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 152:833–842
34. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B (2005) The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression—a replication. Arch Gen Psychiatry 62:529–535
35. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ (1992) Major depression and generalised anxiety disorder. Same genes, (partly) different environments? Arch Gen Psychiatry 49:716–722
36. Kessler R, McGonagle KA, Zhao CB, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Study. Arch Gen Psychiatry 51:8–19
37. Kessler RC, Chiu WT, Demler O, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:617–627
38. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG (1996) Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 168:17–30
39. Lau JYF, Gregory AM, Goldwin MA, Pine DS, Eley TC (2007) Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. Dev Psychopathol 19:1129–1246
40. Levinson DF (2006) The genetics of depression: a review. Biol Psychiatry 60:84–92
41. Lieb R, Becker E, Altamura C (2005) The epidemiology of generalised anxiety disorder in Europe. Eur Neuropsychopharmacol 15:445–452
42. Mackintosh MA, Gatz M, Wetherell JL, Pedersen NL (2006) A twin study of lifetime generalised anxiety disorder (GAD) in older adults: genetic and environmental influences shared by neuroticism and GAD. Twin Res Hum Genet 9:30–37
43. Malhotra AK, Murphy GM, Kennedy JL (2004) Pharmacogenetics of psychotropic drug response. Am J Psychiatry 161:780–796
44. McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJR, Fromm S, Charney DS, Leibenluft E, Ernst M, Pine DS (2007) Abnormal attention modulation of fear circuit function in pediatric generalised anxiety disorder. Arch Gen Psychiatry 64:97–106
45. Meyer TJ, Miller ML, Metzger RL, Borkovec TD (1990) Development and validation of the Penn State Worry Questionnaire. Behav Res Ther 28:487–495
46. Moffitt TE, Caspi A, Rutter M (2005) Strategy for investigating interactions between measured genes and measured environments. Arch Gen Psychiatry 62:473–481
47. Moffitt TE, Harrington HL, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, Poulton R (2007) Depression and generalised anxiety disorder: cumulative and sequential cormobidity in a birth cohort followed to age 32. Arch Gen Psychiatry 64:651–660
48. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, Blair RJR, Chen G, Charney DS, Ernst M, Pine DS (2006) Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalised anxiety disorder. Am J Psychiatry 163:1091–1097
49. Nutt DJ, Ballenger JC, Sheehan D, Wittchen HU (2002) Generalised anxiety disorder: comorbidity, comparative biology and treatment. Int J Neuropsychopharmacol 5:315–325
50. Ohara K, Suzuki Y, Ochiai M, Tsukamoto T, Tani K (1999) A variable-number-tandem-repeat of the serotonin transporter gene and anxiety disorders. Prog Neuropsychopharmacol Biol Psychiatry 23:55–65
51. Pike A, McGuire S, Hetherington EM, Reiss D, Plomin R (1996) Family environment and adolescent depressive symptoms and antisocial behavior: a multivariate genetic analysis. Dev Psychol 32:590–603
52. Plomin R, DeFries JC, McClearn GE, McGuffin P (2001) Behavioral Genetics. 4th edn. Worth Publishers, New York
53. Purcell S (2002) Variance components models for gene-environment interaction in twin analysis. Twin Res 5:554–571
54. Roemer L, Borkovec M, Posa S, Borkovec TD (1995) A self-report diagnostic measure of generalised anxiety disorder. J Behav Ther Exp Psychiatry 26:345–350
55. Roy MA, Neale MC, Pedersen NL, Mathe AA, Kendler KS (1995) A twin study of generalised anxiety disorder and major depression. Psychol Med 25:1037–1049
56. Rutter M (2006) Genes and behavior. Blackwell, Oxford, pp 199–200
57. Samochowiec J, Hajduk A, Samochowiec A, Horodnicki J, Stepien G, Grzywacz A, Kucharska-Mazur J (2004) Association studies of MAO-A, COMT, and 5-HTT genes polymorphisms in patients with anxiety disorders of the phobic spectrum. Psychiatry Res 128:21–26
58. Silberg J, Rutter M, Neale M, Eaves L (2001) Genetic moderation of environmental risk for depression and anxiety in adolescent girls. Br J Psychiatry 179:116–121
59. Surtees PG, Wainwright NWJ, Willis-Owen SAG, Luben R, Day NE, Flint J (2006) Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. Biol Psychiatry 59:224–229
60. Tadic A, Rujescu D, Szegedi A, Giegling I, Singer P, Moller HJ, Dahmen N (2003) Association of a MAOA gene variant with generalised anxiety disorder, but not with panic disorder or major depression. Am J Med Genet B Neuropsychiatr Genet 117B: 1–6
61. Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, Axelson D, Whalen PJ, Casey BJ (2001) Amygdala response to fearful faces in anxious and depressed children. Arch Gen Psychiatry 58:1057–1063
62. Wilhelm K, Mitchell PB, Niven H, Finch A, Wedgwood L, Scimone A, Blair IP, Parker G, Schofield PR (2006) Life events, first depression onset and the serotonin transporter gene. Br J Psychiatry 188:210–215
63. Wittchen HU, Zhao SY, Kessler RC, Eaton WW (1994) DSM-III-R Generalised Anxiety Disorder in the National-Comorbidity-Survey. Arch Gen Psychiatry 51:355–364
64. You JS, Hu SY, Chen BL, Zhang HG (2005) Serotonin transporter and tryptophan hydroxylase gene polymorphisms in Chinese patients with generalised anxiety disorder. Psychiatr Genet 15:7–11