Psychological Medicine

cambridge.org/psm

Invited Review

All authors contributed equally to this work.

Cite this article: Ask H, Cheesman R, Jami ES, Levey DF, Purves KL, Weber H (2021). Genetic contributions to anxiety disorders: where we are and where we are heading. *Psychological Medicine* **51**, 2231–2246. https://doi.org/10.1017/S0033291720005486

Received: 30 September 2020
Revised: 21 December 2020
Accepted: 5 January 2021
First published online: 9 February 2021

Key words:
Anxiety disorders; genetics; internalising; heritability

Author for correspondence:
Helga Ask, E-mail: helga.ask@fhi.no

Genetic contributions to anxiety disorders: where we are and where we are heading

Helga Ask[1], Rosa Cheesman[2,3], Eshim S. Jami[4,5], Daniel F. Levey[6,7], Kirstin L. Purves[3] and Heike Weber[8]

[1]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway; [2]PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway; [3]Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [4]Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [5]Department of Clinical, Educational and Health Psychology, Division of Psychology and Language Sciences, University College London, London, UK; [6]Division of Human Genetics, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut; [7]Department of Psychiatry, Veterans Affairs Connecticut Healthcare Center, West Haven, Connecticut and [8]Department of Psychology, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

Abstract

Anxiety disorders are among the most common psychiatric disorders worldwide. They often onset early in life, with symptoms and consequences that can persist for decades. This makes anxiety disorders some of the most debilitating and costly disorders of our time. Although much is known about the synaptic and circuit mechanisms of fear and anxiety, research on the underlying genetics has lagged behind that of other psychiatric disorders. However, alongside the formation of the Psychiatric Genomic Consortium Anxiety workgroup, progress is rapidly advancing, offering opportunities for future research.

Here we review current knowledge about the genetics of anxiety across the lifespan from genetically informative designs (i.e. twin studies and molecular genetics). We include studies of specific anxiety disorders (e.g. panic disorder, generalised anxiety disorder) as well as those using dimensional measures of trait anxiety. We particularly address findings from large-scale genome-wide association studies and show how such discoveries may provide opportunities for translation into improved or new therapeutics for affected individuals. Finally, we describe how discoveries in anxiety genetics open the door to numerous new research possibilities, such as the investigation of specific gene–environment interactions and the disentangling of causal associations with related traits and disorders.

We discuss how the field of anxiety genetics is expected to move forward. In addition to the obvious need for larger sample sizes in genome-wide studies, we highlight the need for studies among young people, focusing on specific underlying dimensional traits or components of anxiety.

Introduction

The field of psychiatric genetics is rapidly advancing our knowledge of genetic influences on mental health. Whilst great progress has been made in genomic discovery for disorders such as major depressive disorder (MDD) (Howard et al., 2019; Wray et al., 2020) and schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020), few well-powered genomic investigations of anxiety disorders have been undertaken (see Fig. 1). A major driver for genetic discoveries has been the work of the Psychiatric Genomics Consortium (PGC) in conducting genome-wide association studies (GWAS) meta-analyses since 2007. Pending the upcoming first freeze of the PGC Anxiety workgroup, an overview of progress in anxiety disorder genetics is timely. This review draws on well-established findings from twin literature and contributions from molecular genomic approaches to describe the role of genes on anxiety phenotypes across the lifespan and identify potential pitfalls and promises for the developing field of anxiety disorder genetics.

Definition of illness

Anxiety describes an unpleasant and negative state that is a universal part of the human experience. It is characterised by feelings of unease, tension and worry alongside physiological arousal in anticipation of threat or in the face of ambiguity (Lewis, 1970). It can exist as a transitory experience (state) or as a general predisposition to respond anxiously in any given situation (trait) (Spielberger, 1985). Historically, anxiety has been described as central to all

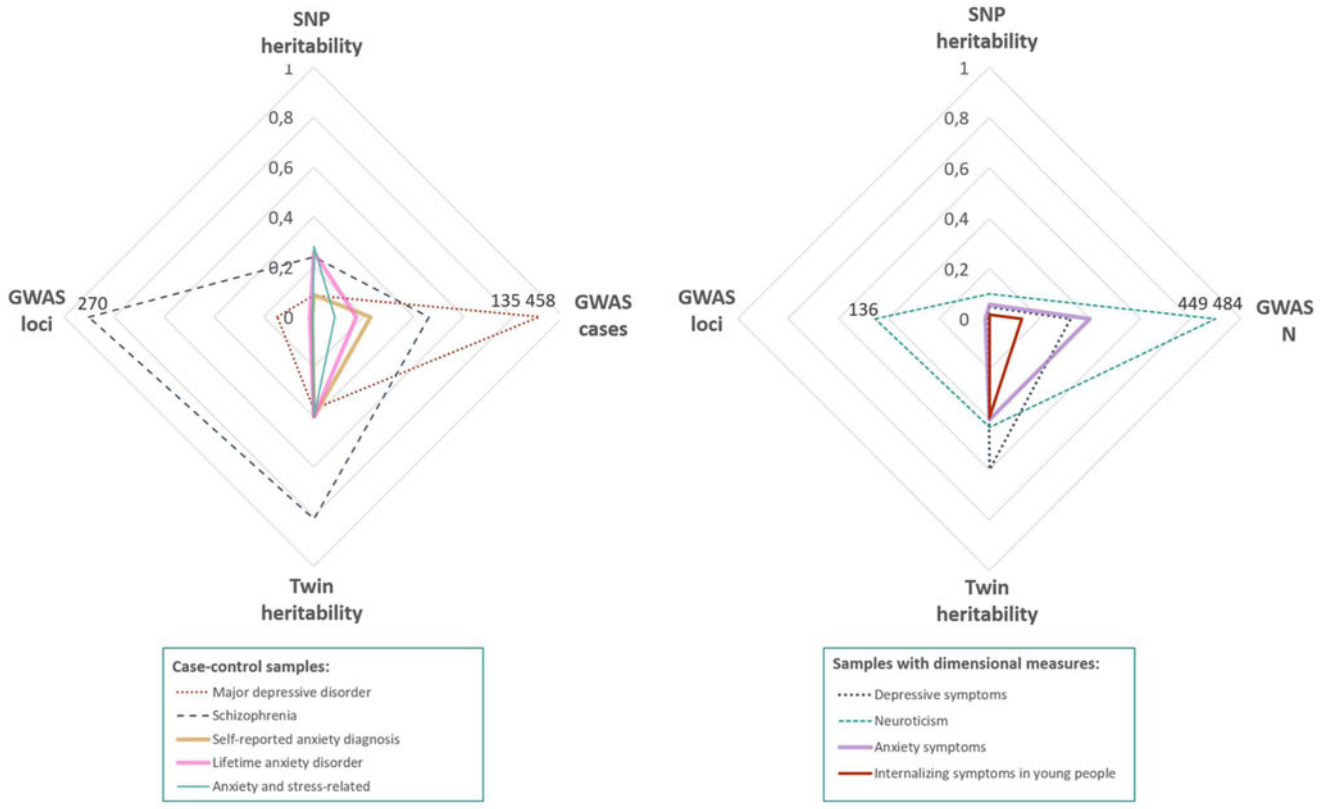

Fig. 1. Heritability, GWAS sample size and number of detected loci. Radar plots comparing current genetic findings for anxiety disorder (left) and dimensions (right) with other psychiatric phenotypes. Major depressive disorder (MDD), depressive symptoms and neuroticism were selected for their high phenotypic and genetic overlap with anxiety disorders. Schizophrenia was selected as the psychiatric disorder with the largest sample size to date. For disorders with lower heritability (e.g. anxiety disorders, MDD), a higher number of cases is needed in order to detect significant loci. Notably, SNP heritability in anxiety is generally higher than expected based on other disorders. GWAS references: Self-reported anxiety diagnosis and Anxiety symptoms (Levey et al., 2020); Lifetime anxiety disorder (Purves et al., 2019); Anxiety and stress-related diagnosis (Meier et al., 2019); Major depressive disorder (Wray et al., 2020); Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020); Depressive symptoms (Okbay et al., 2016); Neuroticism (Nagel et al., 2018a); Internalising symptoms (Jami et al., 2020). Twin heritability references: (Meier & Deckert, 2019; Sullivan, Neale, & Kendler, 2000, 2020; Vukasović & Bratko, 2015).
Note: GWAS *N* and GWAS cases were scaled dividing by 500 000 and 150 000, respectively, GWAS significant loci was scaled dividing by 300.

psychopathology (Freud, 1926/1959). Although fear and anxious feelings can be adaptive (Lee, Wadsworth, & Hotopf, 2006), intense, prolonged or disproportionate experience of it is harmful and maladaptive. The third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) published in 1980 was the first of the series to identify anxiety disorders as a diagnostic category rather than as a symptom of another disorder (Crocq, 2015). Most recently, the fifth edition of the DSM differentiates an anxiety disorder from normative and developmentally appropriate fear or anxiety if it is excessive (i.e. disproportionate to the triggering event), non-transient (i.e. typically continues for several months), and causes significant distress or impairment (American Psychiatric Association, 2013a).

This review will focus primarily on these disproportionate and disordered experiences of anxiety, whilst acknowledging studies examining trait anxiety as a dimensional construct that transcends diagnostic boundaries. Anxiety disorders consist of seven core disorders (see description Fig. 2). Selective mutism and separation anxiety are predominantly restricted to childhood, while the other five subtypes [Generalised Anxiety Disorder (GAD), Social Anxiety Disorder, Panic Disorder (PD), Specific Phobia and Agoraphobia] occur across the lifespan. Although Post-traumatic Stress Disorder and Obsessive-Compulsive Disorders were classified as anxiety disorders in both the DSM-iii and DSM-iv, they have since been reclassified as Obsessive-Compulsive and related, and Trauma and stressor-related disorders respectively, and will not be included in this review.

Epidemiology

Anxiety disorders are amongst the most frequently occurring mental health disorders in adulthood (Kupfer, 2015) and adolescence (Kessler et al., 2012a), with a global lifetime prevalence of 16% (Kessler et al., 2009). The median age of onset for any anxiety disorder is before mid-adolescence (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), with the average age of onset varying widely depending on the specific subtype studied (see Fig. 2). The disorders often have a chronic course across the lifespan (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2017; Kendler et al., 2011; Nivard et al., 2015a; Waszczuk, Zavos, Gregory, & Eley, 2016). There are clear sex differences in the epidemiology of anxiety. Anxiety disorders and symptoms occur more often in women than men with the exception of social phobia (Craske, 2003), and the odds of developing any anxiety disorder during the lifetime is 1.7 times greater for women than men (McLean, Asnaani, Litz, & Hofmann, 2011).

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

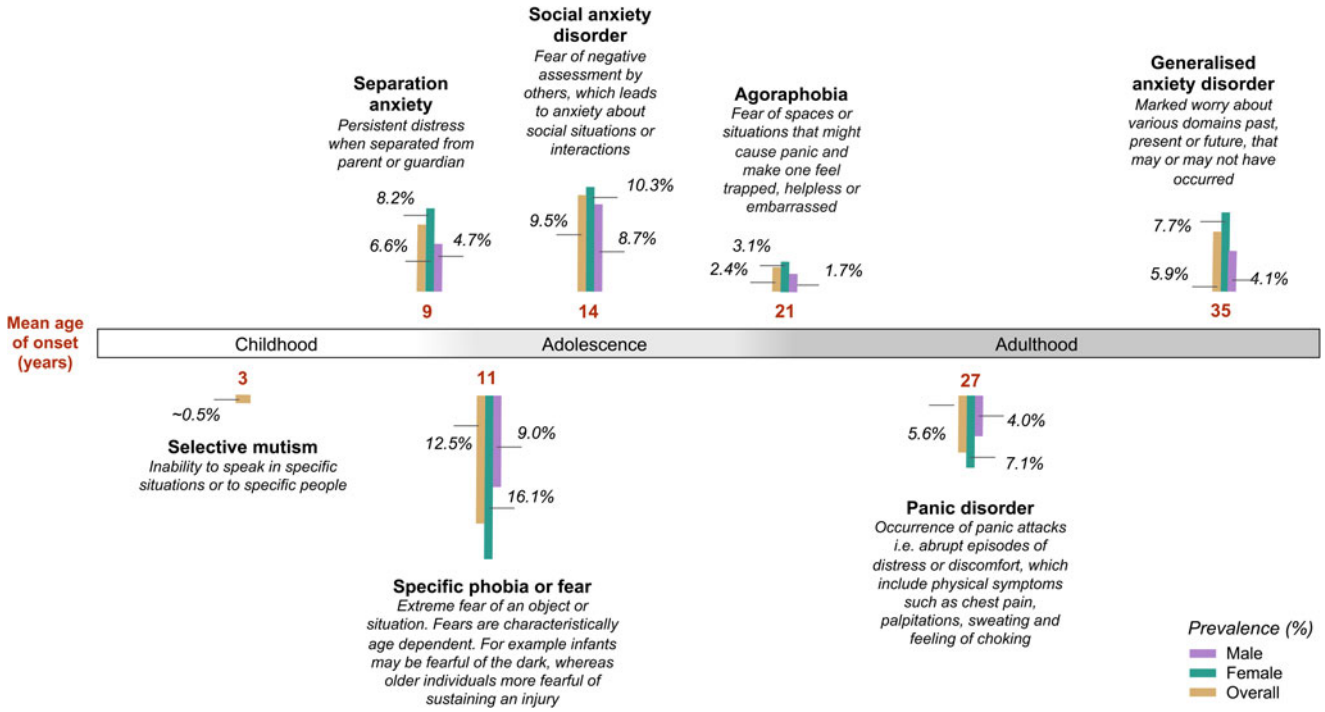

Fig. 2. Anxiety disorder subtypes, age of onset (de Lijster et al., 2017) and lifetime prevalence (%) in males and females (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012b; McLean et al., 2011; Viana, Beidel, & Rabian, 2009).

Risk factors

Anxiety disorders are complex, influenced by a combination of genetic and environmental factors. As with most psychiatric disorders, genetic influences are amongst the best-substantiated risk factors. Although differences in brain structure, function, and connectivity have been demonstrated with some consistency (Craske et al., 2017), it is still unclear to what extent such neural differences are driven by genetic variation, environmental exposures, the experience of anxiety over time, or some interplay of these factors.

Environmental stressors and specific learning experiences may increase the risk for developing anxiety disorders (Beesdo, Knappe, & Pine, 2009; Rachman, 2019, 1990, 1991). The leading etiologic model for anxiety disorders to date is the diathesis-stress hypothesis which suggests that genes and environmental stressors, independently and in combination, increase individuals' liability to developing a disorder. Environmental factors associated with an increased risk for anxiety disorder include low socioeconomic status, parental conflict, childhood maltreatment, the death of a parent, and threat exposure (Beesdo et al., 2009). Such factors may lead to learning experiences linked with later anxiety disorder including direct or vicarious (observation of others) exposure to threat, and receipt of negative or threatening information through word of mouth or media (Askew & Field, 2008; Field, Argyris, & Knowles, 2001; Ollendick & King, 1991; Rachman, 2019, 1990, 1991).

It is important to note that psychological and environmental factors are themselves somewhat heritable (Zavos, Rijsdijk, Gregory, & Eley, 2010) and genetic expression might be shaped by the environment and life experiences via gene–environment interplay. Thus, observed associations between environmental factors and anxiety may reflect the effects of genetic and environmental confounding factors rather than underlying causal relationships. Research seeking to disentangle the direction of causality could be guided by the diathesis-stress model or the differential susceptibility theory (Belsky, 2016) whereby individuals differ in their sensitivity to both negative and positive environmental influences.

Morbidity and mortality

Anxiety disorders are one of the top 10 leading causes of non-fatal disability globally when accounting for prevalence, chronicity, high rates of comorbidity and the severity and likelihood of disorder sequelae (GBD, 2017 Disease & Injury Incidence & Prevalence Collaborators, 2018). Anxiety disorders are also associated with significant higher mortality rates compared to those without a psychiatric diagnosis (Lecrubier, 2007; Meier et al., 2019; Nepon, Belik, Bolton, & Sareen, 2010). A prospective study using nationwide Danish register data (Meier et al., 2019) identified increased mortality rate ratios due to both natural (1.39 95% CI 1.28–1.51) and unnatural (2.46 95% 2.20–2.73) causes when adjusted for demographic characteristics, somatic comorbidity and depressive disorders. Notably, much of the increased risk was explained by the high rate of comorbid mental and physical disorders, particularly MDD (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Meier et al., 2019; Miloyan, Bulley, Bandeen-Roche, Eaton, & Gonçalves-Bradley, 2016).

Untreated, anxiety disorders can persist for decades and cause great impairment in general functioning; adversely influencing social relationships, academic achievements, and employability (Erskine et al., 2015). Effective treatment options for anxiety disorders include both psychotherapy and pharmacological approaches (Bandelow, Michaelis, & Wedekind, 2017). Nonetheless, each second adult and third child fail to respond

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

to existing treatments (Loerinc et al., 2015; Strawn & Levine, 2020), and few remain in remission (Rosenbaum, 2019). Furthermore, many individuals who suffer from anxiety do not seek and/or receive treatment (Rayner et al., 2019a).

Comorbidities

According to Kessler et al. (2005), anxiety disorders commonly co-occur and the authors identified tetrachoric correlations among different anxiety disorders, particularly between PD and agoraphobia (0.64), other specific phobias (0.49) and GAD (0.46). High current and lifetime comorbidity are also observed with other psychiatric disorders. Of particular interest is the high overlap with depression (including depressive symptoms, subthreshold depressive disorders and MDD) throughout the lifespan. Over 50% of individuals with depressive disorders report a history of an anxiety disorder (Hirschfeld, 2001). The substantial overlap has also been observed with other stress-related disorders (post-traumatic stress disorder, obsessive-compulsive disorder), alcohol and substance abuse disorders, and attention deficit/hyperactivity disorder (Kessler et al., 2005). Anxiety disorders are also comorbid with many somatic conditions including epilepsy (Gandy et al., 1959), irritable bowel syndrome (Zamani, Alizadeh-Tabari, & Zamani, 2019), cardiovascular disease (Celano, Daunis, Lokko, Campbell, & Huffman, 2016), and cancers (Kuhnt et al., 2016). Comorbid anxiety disorder in chronic medical disorders like cardiovascular diseases and cancer is associated with a worse prognosis (Celano et al., 2016; Hernández Blázquez & Cruzado, 2016; Kuhnt et al., 2016; Pasquini et al., 2006).

Genetic epidemiology

Twin studies of anxiety disorders

Twin studies provide an elegant natural experiment to investigate relative influences of genetic and environmental factors on psychiatric disorders. The classical twin design compares the phenotypic similarity between monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ twins share 100% of their segregating genes, whereas DZ twins share 50%. Both MZ and DZ twins share the same rearing environment. Using this information, it is possible to estimate the extent of variation in anxiety due to three latent influences: genetics, shared environment (influences that increase familial resemblance), and non-shared environment (influences that make family members different from one another) (Neale & Cardon, 1992). Heritability is the proportion of phenotypic variance that can be explained by genetic variation in the population under study. Twin heritability estimates of anxiety disorders are consistently low to moderate (20–60%) across subtypes (Hettema, Neale, & Kendler, 2001; Polderman et al., 2015). Environmental variance is primarily non-shared and accounts for the variance are not attributable to genetics. Shared environmental influence is often detected in childhood but declines during adolescence and is generally absent in adult anxiety (Cheesman, Rayner, & Eley, 2019; Nivard et al., 2015a).

Developmental twin studies of anxiety dimensions

Developmental twin studies of anxiety show that genes are important for both the full range of dimensional anxiety-related traits (e.g. *internalising symptoms* or *emotional problems*) in young people and youth anxiety disorders (Polderman et al., 2015). It is important to understand whether anxiety symptoms and disorders reflect the same underlying genetics, and how genetic risk for anxiety-related traits in young people relates to the underlying genetics of adult disorders. Research on common psychiatric behaviours suggests that vulnerability factors exist on a continuum, with anxiety disorders representing the extremes of quantitative dimensions (Plomin, Haworth, & Davis, 2009). Heritability estimates of childhood and adult anxiety measures are similar (Polderman et al., 2015). Longitudinal twin studies suggest that the moderate stability of anxiety (and depression) phenotypes from childhood through to adulthood is predominantly influenced by stability in genetic influences (Hannigan et al., 2017; Nivard, Middeldorp, Dolan, & Boomsma, 2015b; Waszczuk et al., 2016). Some genetic innovation influences temporal change in anxiety behaviours in childhood and early adolescence, but these new influences wane in later adolescence (Hannigan et al., 2017). Once individuals reach adulthood, there is more evidence for the stability of genetic effects over time (McGrath, Weill, Robinson, Macrae, & Smoller, 2012).

The genetic structure of anxiety disorders

On the phenotypic level, anxiety disorder subtypes typically fit a 2-factor model characterised by distress (GAD and MDD) and fear (PD and specific phobias) (Krueger, 1999; Watson, 2005). Multivariate twin studies have found limited evidence to support this model on the genetic level. Studies are consistent in that GAD and PD (i.e. distress and fear disorders) share a genetic basis, whereas at least some subtypes of phobias are influenced by other genetic factors (Hettema, Prescott, Myers, Neale, & Kendler, 2005; Tambs et al., 2009). Interestingly, preliminary genome-wide evidence supports the distress and fear distinction in anxiety disorders (Morneau-Vaillancourt et al., 2020). Importantly, the genetic structure of anxiety disorders changes across development. One study supported the distress and fear model in adults, but different structures in younger age ranges (Waszczuk, Zavos, Gregory, & Eley, 2014).

Sex differences

Genetic differences do not appear to explain gender differences observed in epidemiological studies. Twin data indicate that the same genetic liability underpins anxiety disorders across sexes, but in females only there is a small influence of the shared environment (Hettema et al., 2001). However, the absence of sex differences may be due to limited statistical power (Kendler, Jacobson, Myers, & Prescott, 2002). In young people, there is mixed evidence for genetic sex differences in anxiety (Franić, Middeldorp, Dolan, Ligthart, & Boomsma, 2010; Lamb et al., 2010; Rice, Harold, & Thapar, 2002). More systematic, well-powered research is needed to fully ascertain the role of genes in sex differences.

Gene–environment interplay

Gene–environment interplay is likely to be important in the phenotypic manifestation of genetic risk for anxiety. Twin studies provide examples of environmentally contingent genetic effects (gene-environment interaction) and genetic influence on exposure to the environment (gene–environment correlation) (Plomin, DeFries, & Loehlin, 1977). These studies have primarily focused on dimensions of anxiety in young people rather than case-control disorders in adults. One replicated

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

example of gene–environment interaction is that genetic risk for early anxiety symptoms enhances sensitivity to adverse life events in adolescent females (Eaves, Silberg, & Erkanli, 2003; Silberg, Rutter, Neale, & Eaves, 2001). With regard to gene–environment correlation, there is some evidence that genes involved in adolescent anxiety evoke elevated parental negativity (McAdams, Gregory, & Eley, 2013).

Molecular genetics

Over the past two decades, molecular genetics research on anxiety disorders has largely been focused on candidate genes. However, due to small sample sizes, phenotypic heterogeneity and the genetic complexity of anxiety disorders, this gene-finding approach has had limited success and results have not been reproducible (Schumacher et al., 2011; Smoller, 2016). The genetic liability to common and complex disorders is likely highly polygenic, influenced by a large number of polymorphisms with only moderate to small effect sizes. Rather than limiting the search to hypothesised candidates, the GWAS enables search for risk variants across the genome (Duncan, Ostacher, & Ballon, 2019).

Genome-wide association studies

The most well-researched source of genetic variation known to influence the risk of psychiatric disorders are single nucleotide polymorphisms (SNPs). GWAS estimate the association between such common genetic variants spread across the genome and a specific trait or disorder. GWAS on specific anxiety disorders and anxiety-relevant traits were for a long time severely underpowered and characterised by mostly negative (Forstner et al., 2019; Hettema et al., 2020; Walter et al., 2013) or inconsistent results (Dunn et al., 2017; Otowa et al., 2009, 2010, 2012, 2014; Stein et al., 1985; Trzaskowski et al., 2013). However, some genome-wide significant and replicated findings were reported like the *Transmembrane Protein 132D* (*TMEM132D*) (Erhardt et al., 2011, 2012; Otowa et al., 2014) for PD, *Fox-1 Homolog A* (*RBFOX1*) (Davies et al., 2015; Otowa et al., 2016) for anxiety sensitivity and *Glycine Receptor Beta* (*GLRB*) gene (Deckert et al., 2017; Kaabi et al., 2006) for agoraphobia symptoms (see Table 1).

To overcome sample size limitations, researchers started analysing disorder subtypes together. By meta-analysing the results of seven GWAS on five clinically ascertained anxiety disorder subtypes, the ANGST Consortium study (Otowa et al., 2016) identified two genome-wide significant loci. The first resulted from a case-control approach ($n = 17\,310$) and mapped to a non-coding RNA on chromosome 3q12. The second region located in the *Calmodulin-Lysine N-Methyltransferase* (*CMKMT*) gene was associated with an anxiety quantitative factor score ($n = 18\,186$). A Danish national register study (iPSYCH) (Meier et al., 2019) performed a GWAS combining anxiety disorders and other stress-related disorders ($n = 31\,880$). This analysis revealed three genome-wide significant SNPs; of those, one mapped to the *Phosphodiesterase 4B* (*PDE4B*) gene, which has been shown to impact anxiety-like behaviour in mice (Zhang et al., 2008).

The largest GWAS of composite anxiety phenotypes used self-reported symptoms and diagnoses to create a binary measure of lifetime anxiety disorder ($n = 83\,566$) and a dimensional measure of current GAD symptoms ($n = 77\,125$) in participants of the UK Biobank (Purves et al., 2019). For lifetime anxiety disorder, five variants reached genome-wide significance with three implicated in regions coding for the proteins *Neurotrophic Receptor Tyrosine Kinase 2* (*NTRK2*), *Transmembrane Protein 106B* (*TMEM106B*) and *Myosin Heavy Chain 15* (*MYH15*) and two within intergenic regions on chromosome 5q15 and 9p23. Arguably the most promising finding of this study is the implication of the *NTRK2* gene, a receptor of *BDNF* playing an essential role in brain function (Andero, Choi, & Ressler, 2014; Correia et al., 2010). GWAS of GAD symptoms replicated the 9p23 locus as described above, which has also been implicated in GWAS of MDD (Wray et al., 2020) and neuroticism (Okbay et al., 2016; Smith et al., 2016).

The largest anxiety GWAS to date was performed in 175 163 European and 24 448 African US military veterans from the Million Veteran Program (MVP) using a 2-item dimensional measure of GAD (GAD-2) (Levey et al., 2020). The authors also conducted a GWAS on a binary measure of self-reported anxiety disorder diagnosis comprising 192 256 European and 23 074 African American participants. The GAD-2 GWAS resulted in six genome-wide loci mapping to the *SATB Homeobox 1* (*SATB1*), *Estrogen Receptor 1* (*ESR1*), *Leucine-Rich-Repeats and IQ Motif Containing 3* (*LPRIQ3*), *Mitotic Arrest Deficient 1 Like 1* (*MAD1L1*) and *Transcription Elongation Factor A2* (*TCEA2*) gene in the European and the *Transient Receptor Potential Cation Channel Subfamily V Member 6* (*TRPV6*) gene in the African American subgroup. One interesting candidate is *SATB1* which, additionally to many other genes, regulates expression of *Corticotropin Releasing Hormone Receptor 1* (*CRHR1*), known as a key regulator of the HPA axis mediated stress/anxiety response (Balamotis et al., 2012; Weber et al., 2016). Two further genome-wide significant loci in the region of the *Aurora Kinase B* (*AURKB*) and the *MAD1L1* gene were detected in the European case-control analysis (Levey et al., 2020). Replication of significant findings in at least one GWAS on anxiety disorders (Meier et al., 2019; Otowa et al., 2014, 2016; Purves et al., 2019), neuroticism (Nagel et al., 2018a; Okbay et al., 2016; Smith et al., 2016) or MDD (Wray et al., 2020) was successful for *TMEM132D*, *RBFOX1, GLRB, CAMKMT, PDE4B*, *NTRK2*, *TMEM106B*, *MYH15*, *SATB1*, *ESR1*, *LRRIQ3 MAD1L1* and *AURKB* (see Table 2).

GWAS of anxiety dimensions in young people

GWAS studies of anxiety phenotypes in children and adolescents have thus far been unsuccessful in identifying genome-wide significant SNPs (Benke et al., 2014; Jami et al., 2020; Trzaskowski et al., 2013). However, a meta-analysis of childhood and adolescent internalising symptoms (age 3–18 years, $n = 64\,641$) by the CAPICE consortium, identified three significant associated genes: *WNT Family Member 3* (*WNT3*), *C-C Motif Chemokine Ligand 26* (*CCL26*) and *Centromere Protein O* (*CENPO*) (Jami et al., 2020). *WNT3* was previously implicated in GWAS of neuroticism (Nagel et al., 2018a; Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018b) which is strongly genetically correlated (rG = 0.76) with childhood and adolescent internalising symptoms (Jami et al., 2020).

SNP heritability

Estimated SNP heritability of anxiety disorders range from 1.7% (in childhood/adolescence) to 31% (in adulthood) and is below the heritability predicted from twin studies (20–60%). Notably, these estimates are higher than what is reported for some other

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

Table 1. Summary of genome-wide significant loci (GWAS, replication sample or meta-analysis) and their replications with at least nominal significance ($p < 0.05$)

Genome-wide association study (GWAS)								Replication of associated GWAS Loci				
Reference	Phenotype	Ancestry	Sample size	h^2_{SNP}	Marker ID	Strongest Locus *p* value	Nearest Gene	Reference	Phenotype	Sample size	Marker ID	Strongest Locus *p* value
Erhardt, 2011	Panic Disorder (DSM-IV)	European	1824	–	rs7309727	1.2×10^{-7}	*TMEM132D*	Erhardt, 2012	Panic Disorder (ICD-10)	3449	rs7309727	1.1×10^{-8}
								Otowa, 2014	Composite Anxiety Disorders (qFS)	3389	rs2170820	4.6×10^{-6}
								Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs7488998	1.1×10^{-3}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs7311853	1.0×10^{-3}
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs35681688	3.0×10^{-4}
								Wray, 2018	Depression	480 359	rs11060415	5.2×10^{-3}
Davies, 2015	Anxiety Sensitivity (ASI)	European	730 twins	44.45%	rs13334105	4.4×10^{-8}	*RBFOX1*	Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs17664315	3.7×10^{-4}
								Okbay, 2016	Neuroticism (EPQ-R, NEO-PIR)	170 911	rs11640647	8.0×10^{-6}
								Nagel, 2018	Neuroticism (EPQ-R-S, NEO-PIR)	449 484	rs3785237	7.0×10^{-13}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs4786092	9.7×10^{-5}
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs6500909	1.2×10^{-4}
								Wray, 2018	Depression	480 359	rs8063603	6.9×10^{-6}
Deckert, 2017	Agoraphobia Symptoms (ACQ)	German	1370	-	rs 78726293	$3{,}3 \times 10^{-8}$	*GLRB*	Deckert, 2017	Agoraphobia Symptoms (SLC-90)	3845	rs7688285	4.3×10^{-4}
								Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs7488998	4.2×10^{-3}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs62331484	9.6×10^{-3}
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs115254422	0.02
Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	European	21 761	13.8%	rs1709393	$1{,}7 \times 10^{-8}$	*intergenic*	–	–	–	–	–
Otowa, 2016	Composite Anxiety Disorders (qFS)	European	18 186	9.5%	rs1067327	2.9×10^{-9}	*CAMKMT*	Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs804877	2.4×10^{-6}
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs78431149	7.1×10^{-3}
								Hettema, 2019	Composite Anxiety Disorders (SAQ, clinical self-report)	28 950	rs1067394	9.08×10^{-11}

Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	Danmark	31 880	28%	rs1458103	6.2×10^{-8}	intergenic	–	–	–	–	–
					rs113209956	6.4×10^{-8}	intergenic	–	–	–	–	–
					rs7528604	5.4×10^{-11}	*PDE4B*	Otowa, 2011	Panic Disorder (DSM-IV)	638	rs10454453	3.4×10^{-3}
								Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs72674130	1.3×10^{-4}
								Nagel, 2018	Neuroticism (EPQ-R-S, NEO-PIR)	449 484	rs7539350	2.6×10^{-4}
								Wray, 2018	Depression	480 359	rs35130999	1.4×10^{-4}
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs573942	1.2×10^{-4}
Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	European	83 566	26.0%	rs1187280	5.2×10^{-8}	*NTRK2*	Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs2378674	5.1×10^{-3}
								Wray, 2018	Depression	480 359	rs11140773	3.1×10^{-7}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs11793480	1.5×10^{-3}
								Purves, 2019	Neuroticism (EPQ-R-S)	241 883	rs1187280	0.01
					rs 3807866	4.8×10^{-8}	*TMEM106B*	Wray, 2018	Depression	480 359	rs3807866	2.6×10^{-8}
								Purves, 2019	Neuroticism (EPQ-R-S)	241 883	rs3807866	1.2×10^{-4}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs6969722	5.0×10^{-3}
					rs 4855559	3.7×10^{-8}	*MYH15*	Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs2688254	2.0×10^{-4}
								Wray, 2018	Depression	480 359	rs113689582	1.7×10^{-6}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs9845136	1.8×10^{-3}
					rs 2861139	2.6×10^{-9}	*intergenic*	Wray, 2018	Depression	480 359	rs2861139	4.0×10^{-3}
								Purves, 2019	Neuroticism (EPQ-R-S)	241 883	rs2861139	0.03
					rs 10809485	1.6×10^{-12}	*intergenic*	Okbay, 2016	Neuroticism (EPQ-R, NEO-PIR)	170 911	rs4938021	2.1×10^{-10}
								Smith, 2016	Neuroticism (EPQ-R-S)	106 716	rs12378446	9.4×10^{-9}
								Wray, 2018	Depression	480 359	rs10959883	4.0×10^{-4}
								Purves, 2019	Neuroticism (EPQ-R-S)	241 883	rs10959883	9.5×10^{-8}
Purves, 2019	Generalised Anxiety Symptoms (GAD-7)	European	77 125	31.0%	rs17189482	4.2×10^{-9}	*intergenic*	Purves, 2019	Neuroticism (EPQ-R-S)	241 883	rs10959883	9.5×10^{-8}
Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	European	114 091	–	rs10959577	5.5×10^{-10}	*intergenic*	Purves, 2019	Neuroticism (EPQ-R-S)	241 883	rs10959883	9.5×10^{-8}
					rs7723509	4.5×10^{-8}	*intergenic*	–	–	–	–	–
Levey, 2020	Generalised Anxiety Symptoms (GAD-2)	European	175 163	5.6%	rs 4603973	6.2×10^{-11}	*SATB1*	Otowa, 2016	Composite Anxiety Disorders (qFS)	18 186	rs4603973	0.03
								Nagel, 2018	Neuroticism (EPQ-R-S, NEO-PIR)	449 484	rs4390955	5.2×10^{-4}
								Wray, 2018	Depression	480 359	rs1475469	8.0×10^{-3}

(*Continued*)

Table 1. (*Continued.*)

Genome-wide association study (GWAS)								Replication of associated GWAS Loci				
Reference	Phenotype	Ancestry	Sample size	h^2_{SNP}	Marker ID	Strongest Locus *p* value	Nearest Gene	Reference	Phenotype	Sample size	Marker ID	Strongest Locus *p* value
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs9310561	0.02
					rs 6557168	1.3×10^{-9}	*ESR1*	Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs1062577	8.6×10^{-3}
								Wray, 2018	Depression	480 359	rs4870062	1.2×10^{-7}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs6557168	0.01
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs112950253	$8.3 \times \times 10^{-4}$
					rs 12023347	8.9×10^{-9}	*LRRIQ3*	Otowa, 2016	Composite Anxiety Disorders (qFS)	18 186	rs12023347	3.0×10^{-3}
								Nagel, 2018	Neuroticism (EPQ-R-S, NEO-PIR)	449 484	rs12023347	6.9×10^{-4}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs12023347	6.6×10^{-4}
					rs 56226325	2.0×10^{-8}	*MAD1L1*	Otowa, 2016	Composite Anxiety Disorders (DSM-IV)	21 761	rs10224497	0.02
								Nagel, 2018	Neuroticism (EPQ-R-S, NEO-PIR)	449 484	rs56226325	6.6×10^{-8}
								Wray, 2018	Depression	480 359	rs1403175	1.1×10^{-6}
								Meier, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	31 880	rs62442913	3.9×10^{-5}
								Purves, 2019	Composite Anxiety Disorders (DSM-IV, CIDI)	83 566	rs6948971	9.7×10^{-4}
					rs6090040	3.3×10^{-8}	*TCEA2*	–	–	–	–	–
Levey, 2020	Generalised Anxiety Symptoms (GAD-2)	African	24 448		rs575403075	2.8×10^{-8}	*TRPV6*	–	–	–	–	–
Levey, 2020	Composite Anxiety Disorders (clinical self-report)	European	192 256	8.8%	rs35546597	1.9×10^{-8}	*AURKB*	Wray, 2018	Depression	480 359	rs2289590	1.6×10^{-4}
			192 256		rs10534613	4.9×10^{-8}	*MAD1L1*	see above				

qFS, quantitative Factor Score; h^2_{SNP}, SNP heritability.

psychiatric disorders relative to the twin estimates (see Fig. 1). The deviation between twin and SNP estimates can be partly explained by insufficient samples sizes, low diagnostic precision and heterogeneity of anxiety phenotypes, and additionally indicates the involvement of rare variants (population frequency below 1%) (Bandyopadhyay, Chanda, & Wang, 2017; Bourrat, Lu, & Jablonka, 2017; Tam et al., 2019).

Rare variant association studies

Rare variants in psychiatric disorders are often investigated through copy number variation (CNV). This is structural variation in which sections of the genome are repeated, and the number of repeats varies between individuals. In addition, whole exome sequencing is increasingly used to investigate rare variants. However, to date no rare variant associations have been found for anxiety disorders (Gregersen et al., 2016; Kawamura et al., 2011; Morimoto et al., 2020) (See list of preliminary findings in Table 2). This is not surprising as GWAS in anxiety disorders have already shown that more than 100 000 individuals are needed for stable results on common variants and previous studies on rare variants have been far from this sample size. Therefore, more whole genome approaches in much larger samples are required to uncover also the impact of rare variants on anxiety disorders.

Genetic contributions to key comorbidities

One of the most interesting and nosologically revealing ideas in the past decade is how we can use genetic correlations in genome-wide models to understand the nature and patterns underlying complex traits and disorders. These methods have been applied to understanding the genetic contributions to the high rates of comorbidity between anxiety and depressive disorders. Large GWAS of anxiety disorder show strong positive genetic correlations with depressive disorders (rG = 0.78) (Levey et al., 2020; Purves et al., 2019). Strong genetic correlations between adult anxiety disorders (particularly GAD) and depressive disorders have also been previously observed in twin studies (rG = 0.70–1) (Kendler, Gardner, Gatz, & Pedersen, 2007; Roy, Neale, Pedersen, Mathé, & Kendler, 1995). Anxiety disorders and depressive disorders may therefore be manifestations of some shared underlying genetic risk, differentiating phenotypically due to trait-specific environmental influences. While such evidence for genetic overlap between anxiety and depressive disorders mirrors known clinical comorbidities, there is also evidence for anxiety specific genetic influences. In an analysis using multi-trait-based conditional and joint analysis (mtCOJO) (Zhu et al., 2018) GWAS summary statistics for MDD (Wray et al., 2020) were used to condition GWAS summary statistics from dimensional GAD-2 anxiety (Levey et al., 2020). This resulted in diminished but significant observed SNP-based heritability for anxiety symptoms after accounting for MDD (Levey et al., 2020).

Genetic correlations have additionally been observed between anxiety disorder (Purves et al., 2019) and symptoms (Levey et al., 2020), and other psychiatric disorders (schizophrenia, bipolar disorder, ADHD), sleep and insomnia, subjective well-being, as well as cardiometabolic traits and risk factors. Positive genetic correlations have also been observed between anxiety disorders and neuroticism both using molecular (rG ~ 0.70) (Levey et al., 2020; Purves et al., 2019) and quantitative genetic approaches (rG ~ 0.8) (Hettema, Prescott, & Kendler, 2004; Ormel et al., 2013).

Genetic correlations of anxiety across age groups provide insight into common genetic architecture across development. Strong genetic correlations (rG > 0.70) observed between childhood internalising symptoms and adult anxiety and MDD (Jami et al., 2020) indicate that shared genetic risk between anxiety, depression and neuroticism appears to be stable across the lifespan.

When interpreting genetic correlations in general, it is important to note that they might indicate horizontal pleiotropy (the same genes influencing different phenotypes), vertical pleiotropy (genes causing one trait, which in turns influences the other), or biases such as population stratification or assortative mating.

Clinical and therapeutic implications

Whilst to date anxiety genetic research has not been used to inform treatment or clinical decision making, there are several promising routes for translational applications.

Identification of novel treatment targets and therapeutic agents

GWAS results are generally assumed to provide the first step in a discovery pipeline that will ultimately lead to the identification of novel biomarkers or therapeutic agents (Breen et al., 2017; Visscher et al., 2017). However, the path from GWAS results to a new drug is not straightforward. The process of going from a genetic variant to a target gene, from the prioritised gene to functional follow-up, from the biological pathway to clinical trials and regulatory approval of a new drug is both slow and costly (Meier & Deckert, 2019). Whilst we do not yet know whether this approach will result in novel drug discovery for anxiety disorders, there is evidence from other complex disorders that GWAS discoveries can be of therapeutic relevance (Visscher et al., 2017). For example, GWAS have identified known drug targets for disorders like schizophrenia and Type 2 diabetes. Large-scale GWAS results could also translate to pharmacotherapy through drug repositioning, when existing drugs are repurposed for the treatment of other disorders. This could be done by extracting gene-sets associated with a variety of drugs and testing whether these are enriched in the anxiety disorder GWAS results (So et al., 2017, 2019). This approach will become increasingly valuable as newer, larger anxiety disorder GWAS are conducted.

Guiding therapeutic choice

Responses to both psychological therapy and drug treatment for anxiety disorders are heritable phenotypes (Deckert & Erhardt, 2019; Eley, 2014). Knowledge of genetic variants, gene expression, and epigenetic modifications associated with treatment response could therefore guide the development and selection of treatment options targeted to particular groups of patients (stratified medicine). The field of pharmacogenetics (Lesko & Woodcock, 2004) is growing and findings from closely related disorders in this field might be of value for the treatment of anxiety disorders; e.g. genetic component of antidepressant response in MDD (Wigmore et al., 2020). Therapygenetics is another emerging field that may be particularly important given that psychological therapy is the first choice of treatment in anxiety disorders (Lester & Eley, 2013). Therapygenetics is an example of a gene–environment interaction, in which response to an environmental influence (treatment) depends on an individual's genetic makeup. GWAS have been conducted in children and adults undergoing

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

Cognitive Behavioural Therapy for anxiety disorders (Coleman et al., 2016; Keers et al., 2016; Rayner et al., 2019b; Roberts et al., 2017; Ziegler et al., 2019). Unfortunately, these samples are difficult to recruit and retain, and these analyses have so far been underpowered. An ongoing aim of the Anxiety Workgroup of the PGC is to conduct therapygenetics GWAS in large-scale samples with potential to identify novel variants associated with treatment response.

The use of polygenic scores (PGS)

Discoveries from large-scale GWAS are increasingly used to calculate PGS. These reflect individual-level genetic susceptibility for a disorder, by summarising the contribution of all the disorder-associated common genetic variants in a GWAS into a single variable. As genetic data increasingly becomes available as part of health records, such PGS might have direct clinical utility (Wray et al., 2020). PGS have the potential to be applied in community settings to prioritise individuals for screening programs, to contribute to clinical decision-making in individuals seeking medical help, and to contribute to treatment choices for those with an established diagnosis (Wray et al., 2020). Given the low variance currently explained by anxiety disorder PGS (Purves et al., 2019), such direct clinical utility is unlikely in the near future. However, combining PGS with epidemiological modelling in deeply phenotyped longitudinal studies opens the door to research with more immediate translational potential. The phenotypic richness of longitudinal cohort studies (e.g. ALSPAC, Fraser et al., 2013; MoBa, Magnus et al., 2016) provides a unique opportunity to map how genetic risk for anxiety disorders manifests across development (see Hannigan et al., 2020). Another exciting application of PGS is the study of gene–environment interplay in anxiety. This could build on the knowledge of gene–environment interaction and correlation from the twin literature (Plomin, 2014) and recent studies documenting interactions between PGS for MDD and reported trauma (Coleman et al., 2020). Results from PGS studies might generate useful knowledge for the detection of specific at-risk strata and enable discoveries of modifiable environmental factors affecting only individuals at high genetic risk. Such results might provide important knowledge for prevention and intervention efforts and will likely inform advice given to patients and families by healthcare professionals (Breen et al., 2017; Dick et al., 2018; Smoller, 2020).

The identification of causal associations with anxiety disorders

SNPs or PGS robustly associated with putative risk factors for anxiety disorders (e.g. for prenatal inflammation or smoking) can be used as instrumental variables in Mendelian Randomisation (MR) to unravel causal relationships (Burgess, Bowden, Fall, Ingelsson, & Thompson, 2017), as shown in several recently published studies on related disorders. For example, using independent physical activity-related SNPs as instruments, a MR study provides evidence that physical exercise may be an effective prevention strategy for MDD (Choi et al., 2019). The identification of modifiable causal risk factors for anxiety disorders could, in turn, lead to new policy-based or treatment-based interventions. Another benefit of MR studies is providing important clinical insight on diagnostic overlaps and comorbidities between anxiety and other psychiatric or somatic disorders. Using PGS associated with anxiety disorders as instruments could help distinguish between vertical and horizontal pleiotropy in associations with other disorders. One promising study identified weak evidence for anxiety disorders increasing risk of schizophrenia (Jones et al., 2020). Despite the promise of MR approaches, current anxiety disorder GWAS may not yet be sufficiently powered to provide robust instruments for MR approaches. This exciting area will need to be revisited as anxiety samples reach the size and power that have been achieved for other disorders.

Discussion

For a long time, anxiety genetics has lagged behind genetic studies of other psychiatric disorders (Fig. 1). However, results of recent anxiety GWAS (Levey et al., 2020; Meier et al., 2019; Purves et al., 2019) and the GWAS trajectories of psychiatric disorders like schizophrenia and MDD offer encouragement that genetic discoveries build as study samples grow. Increasing sample sizes is, therefore, an obvious next step for anxiety genetics (Domschke & Deckert, 2012; Maron, Lan, & Nutt, 2018; Meier & Deckert, 2019; Ressler, 2020; Shimada-Sugimoto, Otowa, & Hettema, 2015; Smoller, 2016, 2020). The first PGC anxiety GWAS with approximately 40 000 cases and 80 000 controls is currently underway and represents a sample-size increase with the potential to transform the landscape of anxiety disorder genetics. Larger samples in rare variant association studies and epigenome-wide association studies using next generation sequencing are similarly of importance (Morimoto, Ono, Kurotaki, Imamura, & Ozawa, 2020), however, storage requirements and costs are much larger than that for common genotyping arrays.

A common challenge for the whole GWAS literature is the domination of samples of European ancestries and the exclusion of sex chromosomes. Although anxiety GWAS samples have included Hispanic/Latino (Dunn et al., 2017) and African American participants (Levey et al., 2020), the field should continually strive for the inclusion of diverse samples and the study of sex differences given the known difference in prevalence rates between genders. Another general challenge in GWAS are potential biases of SNP effect sizes due to indirect genetic effects, population stratification and assortative mating (Morris, Davies, Hemani, & Smith, 2020). The presence of shared environmental effects in twin studies of anxiety (in which component indirect genetic effects and assortative mating would contribute) suggests that these biases should be accounted for. Excitingly, the rise of family-based genomic datasets (i.e. genotyped siblings and/or parent-offspring trios) and study designs are increasingly available. These will allow causal direct effects of genetic risk factors for anxiety to be estimated more accurately and will provide exciting opportunities to study indirect parental genetic effects in their own right (Davies et al., 2019; Demange et al., 2020; Young, Benonisdottir, Przeworski, & Kong, 2018).

A consequence of collecting larger samples is often 'minimal phenotyping' (Cai, Kendler, & Flint, 2018). Anxiety disorders are phenotypically complex, and the identification of causal variants and their biological relevance is difficult when the GWAS is based on just a few anxiety symptoms (Smoller, 2020). Parallel to maximising sample sizes, the field should strive to increase samples based on deep phenotyping of specific anxiety disorders as well as distress and fear-related traits thought to underlie or to be intermediate phenotypes for anxiety disorders (Montalvo-Ortiz, Gelernter, Hudziak, & Kaufman, 2016; Savage, Sawyers, Roberson-Nay, & Hettema, 2017). This approach could also further our understanding of comorbidities, particularly with depressive

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

Table 2. Summary of strongest associations in genome-wide rare variant association studies and replication samples

Genome-wide rare variant association study (RVAS)						
Reference	Phenotype	Ancestry	Sample size	Marker ID/ Position	Strongest Locus p value	Nearest Gene
Kawamura, 2011	Panic Disorder (DSM-IV)	Japanese	2055	Chr16:31901431-33149454	3.5×10^{-6}*	*IGH, HERCP4, TP53TG3, SLC6A8, SLC6A10P*
Gregersen, 2016	Panic Disorder (ICD-10)	Faroese Island	265	13:73340202	3.3×10^{-6}	*DIS3*
				9:35825541	3.3×10^{-6}	*FAM221B*
				17:60600558	3.4×10^{-5}	*TLK2*
				rs367699700	4.0×10^{-5}	*DCLRE1C*
				rs374546616	4.7×10^{-5}	*SYNCRIP*
				rs138001880	6.7×10^{-5}	*TANC2*
				rs41275735	7.8×10^{-5}	*PPP3CA*
				rs74588252	8.4×10^{-5}	*CNTN6*
Morimoto, 2018	Panic Disorder (DSM-IV, ICD-10)	Japanese	One family with 35 members	Identification of nine common rare protein-altering variants		
	Panic Disorder (DSM-IV)	Japanese	1904	Replication of identified variants did not yield significant results		
	Panic Disorder (DSM-IV)	European	384	Replication of identified variants did not yield significant results		

*Significant after Bonferroni correction of $p < 0.05$.

disorders. One aim of the PGC is to advance discovery beyond standard diagnostic definitions, including the identification of genetically heterogeneous subsets of individuals within disorder case groups. This could for example involve the study of extremely severe cases, or individuals with specific comorbidities.

Lifespan perspective

A lifespan perspective is important for understanding the developmental trajectory of anxiety disorders and leveraging early intervention or preventative strategies. This includes the investigation of when during development specific genetic variants exert their effect and to what extent there are sensitive periods for genetic influences (Smoller et al., 2019). However, rater and age-related heterogeneity in childhood and adolescence present a challenge for developmentally oriented genetic studies that is not easily resolved by increasing sample sizes. Focusing on the common aspect of multiple phenotypic measurements through factor analysis could be a promising solution for overcoming heterogeneous effects. Such an approach is shown to maximise the reliability and heritability of anxiety (Cheesman et al., 2018). However, deriving a stable anxiety phenotype eliminates changes in anxious behaviours over time, which are informative for investigating genetic innovation. Trajectories capturing both phenotypic stability and change over time are more informative from a developmental perspective than cross-sectional assessments or stable phenotypes and could be used as target phenotypes in genetic studies (McGrath et al., 2012). The utility of using developmental trajectories as phenotypes in GWAS studies is yet to be investigated and requires longitudinal samples with reliable measurements of anxiety across the lifespan.

Conclusion

Large-scale consortia collaborations and methodological developments in molecular genetics hold great promise for the future of anxiety genetics research. We expect novel findings on the genetics of anxiety disorders across the lifespan, and on possible gene–environment interplay. Core features of anxiety disorders will likely take the field of anxiety genetics in a different direction from that of other psychiatric disorders. The early age of onset for anxiety disorders highlights the need for studies among young people and across development. Additionally, the phenotypic complexity of anxiety and its subtypes and the high level of shared aetiology with other disorders and traits speak to a need for genetic investigations on putative underlying or intermediate phenotypes as well as related phenotypes. This should include continued investigation of the fear-distress distinction.

Genetic variation predates any behavioural or even neural variation. Understanding the underlying genetic architecture of anxiety and associated phenotypes will pave the way to a better understanding of the complex downstream relationship between genes, brain, behaviours, and environments. The field of anxiety genetics is at a pivotal point of this understanding. It can be hoped that future work will build on existing research to bridge the gaps between disorder, prevention, and treatment.

Acknowledgements. We are grateful to the chairs of the Anxiety Workgroup of the PGC (Jürgen Deckert, Thalia Eley, and John Hettema) for putting together this group of early career researchers in anxiety genetics, and for their valuable comments on an earlier draft of this manuscript. HA was funded by the Research Council of Norway (grant number 274611).

https://doi.org/10.1017/S0033291720005486 Published online by Cambridge University Press

DFL was supported by a NARSAD Young Investigator Grant (grant number 28530) from the Brain & Behavior Research Foundation. ESJ was supported by the European Union's Horizon 2020 research and innovation programme, Marie Sklodowska Curie Actions (grant number 721567). KLP was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Conflict of interest. All authors declare no conflicts of interest.

References

American Psychiatric Association. (2013a). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Andero, R., Choi, D. C., & Ressler, K. J. (2014). BDNF-TrkB receptor regulation of distributed adult neural plasticity, memory formation, and psychiatric disorders. *Progress in Molecular Biology and Translational Science*, *122*, 169–192. https://doi.org/10.1016/B978-0-12-420170-5.00006-4

Askew, C., & Field, A. P. (2008). The vicarious learning pathway to fear 40 years on. *Clinical Psychology Review*, *28*(7), 1249–1265. https://doi.org/10.1016/j.cpr.2008.05.003

Balamotis, M. A., Tamberg, N., Woo, Y. J., Li, J., Davy, B., Kohwi-Shigematsu, T., & Kohwi, Y. (2012). Satb1 ablation alters temporal expression of immediate early genes and reduces dendritic spine density during postnatal brain development. *Molecular and Cellular Biology*, *32*(2), 333–347. https://doi.org/10.1128/MCB.05917-11

Bandelow, B., Michaelis, S., & Wedekind, D. (2017). Treatment of anxiety disorders. *Dialogues in Clinical Neuroscience*, *19*(2), 93–107.

Bandyopadhyay, B., Chanda, V., & Wang, Y. (2017). Finding the sources of missing heritability within rare variants through simulation. *Bioinformatics and Biology Insights*, *11*, 1177932217735096. https://doi.org/10.1177/1177932217735096

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *The Psychiatric Clinics of North America*, *32*(3), 483–524. https://doi.org/10.1016/j.psc.2009.06.002

Belsky, J. (2016). The differential susceptibility hypothesis. *JAMA Pediatrics*, *170*(4), 321. https://doi.org/10.1001/jamapediatrics.2015.4263

Benke, K. S., Nivard, M. G., Velders, F. P., Walters, R. K., Pappa, I., Scheet, P. A., … Early Genetics and Lifecourse Epidemiology Consortium. (2014). A genome-wide association meta-analysis of preschool internalizing problems. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(6), 667–676. e7. https://doi.org/10.1016/j.jaac.2013.12.028

Bourrat, P., Lu, Q., & Jablonka, E. (2017). Why the missing heritability might not be in the DNA. *Bioessays: News and Reviews in Molecular, Cellular and Developmental Biology*, *39*(7), 1700067. https://doi.org/10.1002/bies.201700067.

Breen, G., Li, Q., Roth, B. L., O'Donnell, P., Didriksen, M., Dolmetsch, R., … Edenberg, H. J. (2016). Translating genome-wide association findings into new therapeutics for psychiatry. *Nature Neuroscience*, *19*(11), 1392–1396. https://doi.org/10.1038/nn.4411

Bulik-Sullivan, B., Loh, P.-R., Finucane, H. K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson, N., … Neale, B. M. (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, *47*(3), 291–295. h https://doi.org/10.1038/ng.3211.

Burgess, S., Bowden, J., Fall, T., Ingelsson, E., & Thompson, S. G. (2017). Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. *Epidemiology (Cambridge, Mass.)*, *28*(1), 30–42. https://doi.org/10.1097/EDE.0000000000000559

Cai, N., Kendler, K., & Flint, J. (2018). Minimal phenotyping yields GWAS hits of low specificity for major depression. *BioRxiv*. https://doi.org/10.1101/440735

Celano, C. M., Daunis, D. J., Lokko, H. N., Campbell, K. A., & Huffman, J. C. (2016). Anxiety disorders and cardiovascular disease. *Current Psychiatry Reports*, *18*(11), 101. https://doi.org/10.1007/s11920-016-0739-5

Cheesman, R., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Purves, K. L., Pingault, J.-B., Breen, G., Rijsdij, K. F., Plomin, R., & Eley, T. C. (2018). Extracting stability increases the SNP heritability of emotional problems in young people. *Translational Psychiatry*, *8*(1), 223. https://doi.org/10.1038/s41398-018-0269-5

Cheesman, R., Rayner, C., & Eley, T. (2019). The genetic basis of child and adolescent anxiety. In Compton, SN, Villabø, MA, & Kristensen (Eds), *Pediatric anxiety disorders* (pp. 17–46). London: Elsevier. https://doi.org/10.1016/B978-0-12-813004-9.00003-7.

Choi, K. W., Chen, C.-Y., Stein, M. B., Klimentidis, Y. C., Wang, M.-J., Koenen, K. C., Smoller, J. W., & Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2019). Assessment of bidirectional relationships between physical activity and depression Among adults: A 2-sample mendelian randomization study. *JAMA Psychiatry*, *76*(4), 399–408. https://doi.org/10.1001/jamapsychiatry.2018.4175

Coleman, J. R. I., Lester, K. J., Keers, R., Roberts, S., Curtis, C., Arendt, K., … Eley, T. C. (2016). Genome-wide association study of response to cognitive-behavioural therapy in children with anxiety disorders. *The British Journal of Psychiatry*, *209*(3), 236–243. https://doi.org/10.1192/bjp.bp.115.168229

Coleman, J. R. I., Peyrot, W. J., Purves, K. L., Davis, K. A. S., Rayner, C., Choi, S. W., … Breen, G. (2020). Genome-wide gene-environment analyses of major depressive disorder and reported lifetime traumatic experiences in UK biobank. *Molecular Psychiatry*, *25*(7), 1430–1446. https://doi.org/10.1038/s41380-019-0546-6

Correia, C. T., Coutinho, A. M., Sequeira, A. F., Sousa, I. G., Lourenço Venda, L., Almeida, J. P., … Vicente, A. M. (2010). Increased BDNF levels and NTRK2 gene association suggest a disruption of BDNF/TrkB signaling in autism. *Genes, Brain, and Behavior*, *9*(7), 841–848. https://doi.org/10.1111/j.1601-183X.2010.00627.x

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*, *60*(8), 837–844. https://doi.org/10.1001/archpsyc.60.8.837

Craske, M. G. (2003). Why more women than men?. In MG Craske (Ed.), *Origins of phobias and anxiety disorders* (pp. 175–203). Oxford: Elsevier. https://doi.org/10.1016/B978-008044032-3/50008-3.

Craske, M. G., Rauch, S. L., Ursano, R., Prenoveau, J., Pine, D. S., & Zinbarg, R. E. (2009). What is an anxiety disorder? *Depression and Anxiety*, *26*(12), 1066–1085. https://doi.org/10.1002/da.20633

Craske, M. G., Stein, M. B., Eley, T. C., Milad, M. R., Holmes, A., Rapee, R. M., & Wittchen, H.-U. (2017). Anxiety disorders. *Nature Reviews. Disease Primers*, *3*, 17024. https://doi.org/10.1038/nrdp.2017.24

Crocq, M.-A. (2015). A history of anxiety: From Hippocrates to DSM. *Dialogues in Clinical Neuroscience*, *17*(3), 319–325.

Davies, N. M., Howe, L. J., Brumpton, B., Havdahl, A., Evans, D. M., & Davey Smith, G. (2019). Within family mendelian randomization studies. *Human Molecular Genetics*, *28*(R2), R170–R179. https://doi.org/10.1093/hmg/ddz204

Davies, M. N., Verdi, S., Burri, A., Trzaskowski, M., Lee, M., Hettema, J. M., … Spector, T. D. (2015). Generalised anxiety disorder – A twin study of genetic architecture, genome-wide association and differential gene expression. *Plos One*, *10*(8), e0134865. https://doi.org/10.1371/journal.pone.0134865

Deckert, J., & Erhardt, A. (2019). Predicting treatment outcome for anxiety disorders with or without comorbid depression using clinical, imaging and (epi)genetic data. *Current Opinion in Psychiatry*, *32*(1), 1–6. https://doi.org/10.1097/YCO.0000000000000468

Deckert, J., Weber, H., Villmann, C., Lonsdorf, T. B., Richter, J., Andreatta, M., … Reif, A. (2017). GLRB Allelic variation associated with agoraphobic cognitions, increased startle response and fear network activation: A potential neurogenetic pathway to panic disorder. *Molecular Psychiatry*, *22*(10), 1431–1439. https://doi.org/10.1038/mp.2017.2

de Lijster, J. M., Dierckx, B., Utens, E. M. W. J., Verhulst, F. C., Zieldorff, C., Dieleman, G. C., & Legerstee, J. S. (2017). The age of onset of anxiety disorders. *Canadian Journal of Psychiatry*, *62*(4), 237–246. https://doi.org/10.1177/0706743716640757

Demange, *et al*. (2020). Parental influences on offspring education: indirect genetic effects of non-cognitive skills. Biorxiv. https://doi.org/10.1101/2020.09.15.296236

Dick, D. M., Barr, P. B., Cho, S. B., Cooke, M. E., Kuo, S. I.-C., Lewis, T. J., … Su, J. (2018). Post-GWAS in psychiatric genetics: A developmental perspective on the "other" next steps. *Genes, Brain, and Behavior*, *17*(3), e12447. https://doi.org/10.1111/gbb.12447

Domschke, K., & Deckert, J. (2012). Genetics of anxiety disorders - status quo and quo vadis. *Current Pharmaceutical Design*, *18*(35), 5691–5698. https://doi.org/10.2174/138161212803530781

Duncan, L. E., Ostacher, M., & Ballon, J. (2019). How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. *Neuropsychopharmacology*, *44*(9), 1518–1523. https://doi.org/10.1038/s41386-019-0389-5

Dunn, E. C., Sofer, T., Gallo, L. C., Gogarten, S. M., Kerr, K. F., Chen, C.-Y., … Smoller, J. W. (2017). Genome-wide association study of generalized anxiety symptoms in the hispanic community health study/study of latinos. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *174*(2), 132–143. https://doi.org/10.1002/ajmg.b.32448

Eaves, L., Silberg, J., & Erkanli, A. (2003). Resolving multiple epigenetic pathways to adolescent depression. *Journal of Child Psychology and Psychiatry*, *44*(7), 1006–1014. https://doi.org/10.1111/1469-7610.00185

Eley, T. C. (2014). The future of therapygenetics: Where will studies predicting psychological treatment response from genomic markers lead? *Depression and Anxiety*, *31*(8), 617–620. https://doi.org/10.1002/da.22292

Erhardt, A., Akula, N., Schumacher, J., Czamara, D., Karbalai, N., Müller-Myhsok, B., … Binder, E. B. (2012). Replication and meta-analysis of TMEM132D gene variants in panic disorder. *Translational Psychiatry*, *2*, e156. https://doi.org/10.1038/tp.2012.85

Erhardt, A., Czibere, L., Roeske, D., Lucae, S., Unschuld, P. G., Ripke, S., … Binder, E. B. (2011). TMEM132D, A new candidate for anxiety phenotypes: Evidence from human and mouse studies. *Molecular Psychiatry*, *16*(6), 647–663. https://doi.org/10.1038/mp.2010.41

Erskine, H. E., Moffitt, T. E., Copeland, W. E., Costello, E. J., Ferrari, A. J., Patton, G., … Scott, J. G. (2015). A heavy burden on young minds: The global burden of mental and substance use disorders in children and youth. *Psychological Medicine*, *45*(7), 1551–1563. https://doi.org/10.1017/S0033291714002888

Field, A. P., Argyris, N. G., & Knowles, K. A. (2001). Who's afraid of the big bad wolf: A prospective paradigm to test Rachman's indirect pathways in children. *Behaviour Research and Therapy*, *39*(11), 1259–1276. https://doi.org/10.1016/S0005-7967(00)00080-2

Forstner, A. J., Awasthi, S., Wolf, C., Maron, E., Erhardt, A., Czamara, D., … Schumacher, J. (2019). Genome-wide association study of panic disorder reveals genetic overlap with neuroticism and depression. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0590-2

Franić, S., Middeldorp, C. M., Dolan, C. V., Ligthart, L., & Boomsma, D. I. (2010). Childhood and adolescent anxiety and depression: Beyond heritability. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(8), 820–829. https://doi.org/10.1016/j.jaac.2010.05.013

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., … Lawlor, D. A. (2013). Cohort profile: The Avon Longitudinal Study of parents and children: ALSPAC mothers cohort. *International Journal of Epidemiology*, *42*(1), 97–110. https://doi.org/10.1093/ije/dys066

Freud, S. (1959). Inhibitions, symptoms and anxiety. In J. Strachey (Ed.), *The standard edition of the complete psychological works of Sigmund Freud* (Vol. *20*, pp. 87–131). London: The Hogarth Press. (Original work published 1926).

Gandy, M., Sharpe, L., Perry, K. N., Miller, L., Thayer, Z., Boserio, J., & Mohamed, A. (2013). Rates of DSM-IV mood, anxiety disorders, and suicidality in Australian adult epilepsy outpatients: A comparison of well-controlled versus refractory epilepsy. *Epilepsy & Behavior*, *26*(1), 29–35. https://doi.org/10.1016/j.yebeh.2012.10.023

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Gregersen, N. O., Lescai, F., Liang, J., Li, Q., Als, T., Buttenschøn, H. N., … Demontis, D. (2016). Whole-exome sequencing implicates DGKH as a risk gene for panic disorder in the Faroese population. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *171*(8), 1013–1022. https://doi.org/10.1002/ajmg.b.32464

Hannigan, L. J., Askeland, R. B., Ask, H., Tesli, M., Corfield, E., Ayorech, Z., … Havdahl, A. (2020). Genetic liability for schizophrenia and childhood psychopathology in the general population. *MedRxiv*. https://doi.org/10.1101/2020.05.01.20086215

Hannigan, L. J., Walaker, N., Waszczuk, M. A., McAdams, T. A., & Eley, T. C. (2017). Aetiological influences on stability and change in emotional and behavioural problems across development: A systematic review. *Psychopathology Review*, *4*(1), 52–108. https://doi.org/10.5127/pr.038315

Hernández Blázquez, M., & Cruzado, J. A. (2016). A longitudinal study on anxiety, depressive and adjustment disorder, suicide ideation and symptoms of emotional distress in patients with cancer undergoing radiotherapy. *Journal of Psychosomatic Research*, *87*, 14–21. https://doi.org/10.1016/j.jpsychores.2016.05.010

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *The American Journal of Psychiatry*, *158*(10), 1568–1578. https://doi.org/10.1176/appi.ajp.158.10.1568

Hettema, J. M., Prescott, C. A., & Kendler, K. S. (2004). Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. *The American Journal of Psychiatry*, *161*(9), 1581–1587. https://doi.org/10.1176/appi.ajp.161.9.1581

Hettema, J. M., Prescott, C. A., Myers, J. M., Neale, M. C., & Kendler, K. S. (2005). The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Archives of General Psychiatry*, *62*(2), 182–189. https://doi.org/10.1001/archpsyc.62.2.182

Hettema, J. M., Verhulst, B., Chatzinakos, C., Bacanu, S.-A., Chen, C.-Y., Ursano, R. J., … Stein, M. B. (2020). Genome-wide association study of shared liability to anxiety disorders in Army STARRS. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *183*(4), 197–207. https://doi.org/10.1002/ajmg.b.32776

Hirschfeld, R. M. A. (2001). The comorbidity of major depression and anxiety disorders: Recognition and management in primary care. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(6), 244–254. https://doi.org/10.4088/pcc.v03n0609

Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, *22*(3), 343–352. https://doi.org/10.1038/s41593-018-0326-7

Jami, E. S., Hammerschlag, A. R., Ip, H. F., Allegrini, A. G., Benyamin, B., Border, R., … Middeldorp, C. M. (2020). Genome-wide association meta-analysis of childhood and adolescent internalising symptoms. *MedRxiv*, 2020.09.11.20175026.

Jones, H. J., Martin, D., Lewis, S. J., Davey Smith, G., O'Donovan, M. C, Owen, M. J., … Zammit, S. (2020). A Mendelian randomization study of the causal association between anxiety phenotypes and schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *183*(6), 360–369. http://dx.doi.org/10.1002/ajmg.b.v183.6.

Kaabi, B., Gelernter, J., Woods, S. W., Goddard, A., Page, G. P., & Elston, R. C. (2006). Genome scan for loci predisposing to anxiety disorders using a novel multivariate approach: Strong evidence for a chromosome 4 risk locus. *American Journal of Human Genetics*, *78*(4), 543–553. https://doi.org/10.1086/501072

Kawamura, Y., Otowa, T., Koike, A., Sugaya, N., Yoshida, E., Yasuda, S., … Sasaki, T. (2011). A genome-wide CNV association study on panic disorder in a Japanese population. *Journal of Human Genetics*, *56*(12), 852–856. https://doi.org/10.1038/jhg.2011.117

Keers, R., Coleman, J. R. I., Lester, K. J., Roberts, S., Breen, G., Thastum, M., … Eley, T. C. (2016). A genome-wide test of the differential susceptibility hypothesis reveals a genetic predictor of differential response to psychological treatments for child anxiety disorders.

Psychotherapy and Psychosomatics, *85*(3), 146–158. https://doi.org/10.1159/000444023

Kendler, K. S., Eaves, L. J., Loken, E. K., Pedersen, N. L., Middeldorp, C. M., Reynolds, C., … Gardner, C. O. (2011). The impact of environmental experiences on symptoms of anxiety and depression across the life span. *Psychological Science*, *22*(10), 1343–1352. https://doi.org/10.1177/0956797611417255

Kendler, K. S., Gardner, C. O., Gatz, M., & Pedersen, N. L. (2007). The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. *Psychological Medicine*, *37*(3), 453–462. https://doi.org/10.1017/S0033291706009135

Kendler, K. S., Jacobson, K. C., Myers, J., & Prescott, C. A. (2002). Sex differences in genetic and environmental risk factors for irrational fears and phobias. *Psychological Medicine*, *32*(2), 209–217. https://doi.org/10.1017/s003329170100513x

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., … Wang, P. S. (2009). The global burden of mental disorders: An update from the WHO World Mental Health (WMH) surveys. *Epidemiologia e Psichiatria Sociale*, *18*(1), 23–33. https://doi.org/10.1017/S1121189X00001421

Kessler, R. C., Avenevoli, S., Costello, E. J., Georgiades, K., Green, J. G., Gruber, M. J., … Merikangas, K. R. (2012a). Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Archives of General Psychiatry*, *69*(4), 372–380. https://doi.org/10.1001/archgenpsychiatry.2011.160

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617–627. https://doi.org/10.1001/archpsyc.62.6.617

Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M., & Wittchen, H.-U. (2012b). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research*, *21*(3), 169–184. https://doi.org/10.1002/mpr.1359

Krueger, R. F. (1999). The structure of common mental disorders. *Archives of General Psychiatry*, *56*(10), 921–926. https://doi.org/10.1001/archpsyc.56.10.921

Kuhnt, S., Brähler, E., Faller, H., Härter, M., Keller, M., Schulz, H., … Mehnert, A. (2016). Twelve-Month and lifetime prevalence of mental disorders in cancer patients. *Psychotherapy and Psychosomatics*, *85*(5), 289–296. https://doi.org/10.1159/000446991

Kupfer, D. J. (2015). Anxiety and DSM-5. *Dialogues in Clinical Neuroscience*, *17*(3), 245–246.

Lamb, D. J., Middeldorp, C. M., van Beijsterveldt, C. E. M., Bartels, M., van der Aa, N., Polderman, T. J. C., & Boomsma, D. I. (2010). Heritability of anxious-depressive and withdrawn behavior: Age-related changes during adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(3), 248–255. https://doi.org/10.1016/j.jaac.2009.11.014

Lecrubier, Y. (2007). Widespread underrecognition and undertreatment of anxiety and mood disorders: Results from 3 European studies. *The Journal of Clinical Psychiatry*, *68*(Suppl 2), 36–41.

Lee, W. E., Wadsworth, M. E. J., & Hotopf, M. (2006). The protective role of trait anxiety: A longitudinal cohort study. *Psychological Medicine*, *36*(3), 345–351. https://doi.org/10.1017/S0033291705006847

Lesko, L. J., & Woodcock, J. (2004). Translation of pharmacogenomics and pharmacogenetics: A regulatory perspective. *Nature Reviews. Drug Discovery*, *3*(9), 763–769. https://doi.org/10.1038/nrd1499

Lester, K. J., & Eley, T. C. (2013). Therapygenetics: Using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biology of Mood & Anxiety Disorders*, *3*(1), 4. https://doi.org/10.1186/2045-5380-3-4

Levey, D. F., Gelernter, J., Polimanti, R., Zhou, H., Cheng, Z., Aslan, M., … Stein, M. B. (2020). Reproducible genetic risk loci for anxiety: Results from ~200000 participants in the million veteran program. *The American Journal of Psychiatry*, *177*(3), 223–232. https://doi.org/10.1176/appi.ajp.2019.19030256

Lewis, A. (1970). The ambiguous word "anxiety". *International Journal of Psychiatry*, *9*, 62–79.

Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske, M. G. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clinical Psychology Review*, *42*, 72–82. https://doi.org/10.1016/j.cpr.2015.08.004

Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A. K., … Stoltenberg, C. (2016). Cohort profile update: The Norwegian mother and child cohort study (moba). *International Journal of Epidemiology*, *45*(2), 382–388. https://doi.org/10.1093/ije/dyw029

Maron, E., Lan, C.-C., & Nutt, D. (2018). Imaging and genetic approaches to inform biomarkers for anxiety disorders, obsessive-compulsive disorders, and PSTD. *Current Topics in Behavioral Neurosciences*, *40*, 219–292. https://doi.org/10.1007/7854_2018_49

McAdams, T. A., Gregory, A. M., & Eley, T. C. (2013). Genes of experience: Explaining the heritability of putative environmental variables through their association with behavioural and emotional traits. *Behavior Genetics*, *43*(4), 314–328. https://doi.org/10.1007/s10519-013-9591-0

McGrath, L. M., Weill, S., Robinson, E. B., Macrae, R., & Smoller, J. W. (2012). Bringing a developmental perspective to anxiety genetics. *Development and Psychopathology*, *24*(4), 1179–1193. https://doi.org/10.1017/S0954579412000636

McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research*, *45*(8), 1027–1035. https://doi.org/10.1016/j.jpsychires.2011.03.006

Meier, S. M., & Deckert, J. (2019). Genetics of anxiety disorders. *Current Psychiatry Reports*, *21*(3), 16, 1-8. https://doi.org/10.1007/s11920-019-1002-7

Meier, S. M., Mattheisen, M., Mors, O., Mortensen, P. B., Laursen, T. M., & Penninx, B. W. (2016). Increased mortality among people with anxiety disorders: Total population study. *The British Journal of Psychiatry*, *209*(3), 216–221. https://doi.org/10.1192/bjp.bp.115.171975

Meier, S. M., Trontti, K., Purves, K. L., Als, T. D., Grove, J., Laine, M., … Mors, O. (2019). Genetic variants associated with anxiety and stress-related disorders: A genome-wide association study and mouse-model study. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2019.1119

Miloyan, B., Bulley, A., Bandeen-Roche, K., Eaton, W. W., & Gonçalves-Bradley, D. C. (2016). Anxiety disorders and all-cause mortality: Systematic review and meta-analysis. *Social Psychiatry and Psychiatric Epidemiology*, *51*(11), 1467–1475. https://doi.org/10.1007/s00127-016-1284-6

Montalvo-Ortiz, J. L., Gelernter, J., Hudziak, J., & Kaufman, J. (2016). RDoc and translational perspectives on the genetics of trauma-related psychiatric disorders. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *171B*(1), 81–91. https://doi.org/10.1002/ajmg.b.32395

Morimoto, Y., Ono, S., Kurotaki, N., Imamura, A., & Ozawa, H. (2020). Genetic and epigenetic analyses of panic disorder in the post-GWAS era. *Journal of Neural Transmission*, 127, 1517-1526. https://doi.org/10.1007/s00702-020-02205-y

Morimoto, Y., Shimada-Sugimoto, M., Otowa, T., Yoshida, S., Kinoshita, A., Mishima, H., … Ono, S. (2018). Whole-exome sequencing and gene-based rare variant association tests suggest that PLA2G4E might be a risk gene for panic disorder. *Translational Psychiatry*, *8*(1), 41. https://doi.org/10.1038/s41398-017-0088-0

Morneau-Vaillancourt, G., Coleman, J. R. I., Purves, K. L., Cheesman, R., Rayner, C., Breen, G., & Eley, T. C. (2020). The genetic and environmental hierarchical structure of anxiety and depression in the UK biobank. *Depression and Anxiety*, *37*(6), 512–520. https://doi.org/10.1002/da.22991

Morris, T. T., Davies, N. M., Hemani, G., & Smith, G. D. (2020). Population phenomena inflate genetic associations of complex social traits. *Science Advances*, *6*(16), eaay0328. https://doi.org/10.1126/sciadv.aay0328

Nagel, M., Jansen, P. R., Stringer, S., Watanabe, K., de Leeuw, C. A., Bryois, J., … Posthuma, D. (2018a). Meta-analysis of genome-wide association studies for neuroticism in 449484 individuals identify novel genetic loci and pathways. *Nature Genetics*, *50*(7), 920–927. https://doi.org/10.1038/s41588-018-0151-7

Nagel, M., Watanabe, K., Stringer, S., Posthuma, D., & van der Sluis, S. (2018b). Item-level analyses reveal genetic heterogeneity in neuroticism. *Nature Communications*, *9*(1), 905. https://doi.org/10.1038/s41467-018-03242-8

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Springer Netherlands. https://doi.org/10.1007/978-94-015-8018-2

Nepon, J., Belik, S.-L., Bolton, J., & Sareen, J. (2010). The relationship between anxiety disorders and suicide attempts: Findings from the national epidemiologic survey on alcohol and related conditions. *Depression and Anxiety*, *27*(9), 791–798. https://doi.org/10.1002/da.20674

Nivard, M. G., Dolan, C. V., Kendler, K. S., Kan, K. J., Willemsen, G., van Beijsterveldt, C. E. M., … Boomsma, D. I. (2015a). Stability in symptoms of anxiety and depression as a function of genotype and environment: A longitudinal twin study from ages 3 to 63 years. *Psychological Medicine*, *45*(5), 1039–1049. https://doi.org/10.1017/S003329171400213X

Nivard, M. G., Middeldorp, C. M., Dolan, C. V., & Boomsma, D. I. (2015b). Genetic and environmental stability of neuroticism from adolescence to adulthood. *Twin Research and Human Genetics*, *18*(6), 746–754. https://doi.org/10.1017/thg.2015.80

Okbay, A., Baselmans, B. M. L., De Neve, J.-E., Turley, P., Nivard, M. G., Fontana, M. A., … Cesarini, D. (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nature Genetics*, *48*(6), 624–633. https://doi.org/10.1038/ng.3552

Ollendick, T. H., & King, N. J. (1991). Origins of childhood fears: An evaluation of Rachman's theory of fear acquisition. *Behaviour Research and Therapy*, *29*(2), 117–123. https://doi.org/10.1016/0005-7967(91)90039-6

Ormel, J., Jeronimus, B. F., Kotov, R., Riese, H., Bos, E. H., Hankin, B., … Oldehinkel, A. J. (2013). Neuroticism and common mental disorders: Meaning and utility of a complex relationship. *Clinical Psychology Review*, *33*(5), 686–697. https://doi.org/10.1016/j.cpr.2013.04.003

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., … … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry*, *21*(10), 1485. https://doi.org/10.1038/mp.2016.11

Otowa, T., Kawamura, Y., Nishida, N., Sugaya, N., Koike, A., Yoshida, E., … Sasaki, T. (2012). Meta-analysis of genome-wide association studies for panic disorder in the Japanese population. *Translational Psychiatry*, *2*, e186. https://doi.org/10.1038/tp.2012.89

Otowa, T., Maher, B. S., Aggen, S. H., McClay, J. L., van den Oord, E. J., & Hettema, J. M. (2014). Genome-wide and gene-based association studies of anxiety disorders in European and African American samples. *Plos One*, *9*(11), e112559. https://doi.org/10.1371/journal.pone.0112559

Otowa, T., Tanii, H., Sugaya, N., Yoshida, E., Inoue, K., Yasuda, S., … Sasaki, T. (2010). Replication of a genome-wide association study of panic disorder in a Japanese population. *Journal of Human Genetics*, *55*(2), 91–96. https://doi.org/10.1038/jhg.2009.127

Otowa, T., Yoshida, E., Sugaya, N., Yasuda, S., Nishimura, Y., Inoue, K., … Okazaki, Y. (2009). Genome-wide association study of panic disorder in the Japanese population. *Journal of Human Genetics*, *54*(2), 122–126. https://doi.org/10.1038/jhg.2008.17

Pasquini, M., Biondi, M., Costantini, A., Cairoli, F., Ferrarese, G., Picardi, A., & Sternberg, C. (2006). Detection and treatment of depressive and anxiety disorders among cancer patients: Feasibility and preliminary findings from a liaison service in an oncology division. *Depression and Anxiety*, *23*(7), 441–448. https://doi.org/10.1002/da.20198

Plomin, R. (2014). Genotype-environment correlation in the era of DNA. *Behavior Genetics*, *44*(6), 629–638. https://doi.org/10.1007/s10519-014-9673-7

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, *84*(2), 309–322. https://doi.org/10.1037/0033-2909.84.2.309

Plomin, R., Haworth, C. M. A., & Davis, O. S. P. (2009). Common disorders are quantitative traits. *Nature Reviews. Genetics*, *10*(12), 872–878. https://doi.org/10.1038/nrg2670

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics*, *47*(7), 702–709. https://doi.org/10.1038/ng.3285

Purves, K. L., Coleman, J. R. I., Meier, S. M., Rayner, C., Davis, K. A. S., Cheesman, R., … Eley, T. C. (2019). A major role for common genetic variation in anxiety disorders. *Molecular Psychiatry*, 25, 3292-3303. https://doi.org/10.1038/s41380-019-0559-1

Rachman, S. (1977). The conditioning theory of fear acquisition: A critical examination. *Behaviour Research and Therapy*, *15*(5), 375–387. https://doi.org/10.1016/0005-7967(77)90041-9

Rachman, S. (1990). The determinants and treatment of simple phobias. *Advances in Behaviour Research and Therapy*, *12*(1), 1–30. https://doi.org/10.1016/0146-6402(90)90005-B

Rachman, S. (1991). Neo-conditioning and the classical theory of fear acquisition. *Clinical Psychology Review*, *11*(2), 155–173. https://doi.org/10.1016/0272-7358(91)90093-A

Rayner, C., Coleman, J. R. I., Purves, K. L., Cheesman, R., Hübel, C., Gaspar, H., … Eley, T. C. (2019a). Genetic influences on treatment-seeking for common mental health problems in the UK biobank. *Behaviour Research and Therapy*, *121*, 103413. https://doi.org/10.1016/j.brat.2019.103413

Rayner, C., Coleman, J. R. I., Purves, K. L., Hodsoll, J., Goldsmith, K., Alpers, G. W., … … Eley, T. C. (2019b). A genome-wide association meta-analysis of prognostic outcomes following cognitive behavioural therapy in individuals with anxiety and depressive disorders. *Translational Psychiatry*, *9*(1), 150. https://doi.org/10.1038/s41398-019-0481-y

Ressler, K. J. (2020). Translating across circuits and genetics toward progress in fear- and anxiety-related disorders. *The American Journal of Psychiatry*, *177*(3), 214–222. https://doi.org/10.1176/appi.ajp.2020.20010055

Rice, F., Harold, G. T., & Thapar, A. (2002). Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *43*(8), 1039–1051. https://doi.org/10.1111/1469-7610.00231

Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke, S., Walters, J. T., & O'Donovan, M. C. (2020). Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. *MedRxiv*. https://doi.org/10.1101/2020.09.12.20192922

Roberts, S., Wong, C. C. Y., Breen, G., Coleman, J. R. I., De Jong, S., Jöhren, P., … Eley, T. C. (2017). Genome-wide expression and response to exposure-based psychological therapy for anxiety disorders. *Translational Psychiatry*, *7*(8), e1219. https://doi.org/10.1038/tp.2017.177

Rosenbaum, J. (2019). New directions in anxiety disorder treatment. *General Psychiatry*, *32*(6), e100166. https://doi.org/10.1136/gpsych-2019-100166

Roy, M. A., Neale, M. C., Pedersen, N. L., Mathé, A. A., & Kendler, K. S. (1995). A twin study of generalized anxiety disorder and major depression. *Psychological Medicine*, *25*(5), 1037–1049. https://doi.org/10.1017/s0033291700037533

Savage, J. E., Sawyers, C., Roberson-Nay, R., & Hettema, J. M. (2017). The genetics of anxiety-related negative valence system traits. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *174*(2), 156–177. https://doi.org/10.1002/ajmg.b.32459

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427. https://doi.org/10.1038/nature13595

Schumacher, J., Kristensen, A. S., Wendland, J. R., Nöthen, M. M., Mors, O., & McMahon, F. J. (2011). The genetics of panic disorder. *Journal of Medical Genetics*, *48*(6), 361–368. https://doi.org/10.1136/jmg.2010.086876

Shimada-Sugimoto, M., Otowa, T., & Hettema, J. M. (2015). Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. *Psychiatry and Clinical Neurosciences*, *69*(7), 388–401. https://doi.org/10.1111/pcn.12291

Silberg, J., Rutter, M., Neale, M., & Eaves, L. (2001). Genetic moderation of environmental risk for depression and anxiety in adolescent girls. *The British Journal of Psychiatry*, *179*, 116–121. https://doi.org/10.1192/bjp.179.2.116

Smith, D. J., Escott-Price, V., Davies, G., Bailey, M. E. S., Colodro-Conde, L., Ward, J., … … O'Donovan, M. C. (2016). Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Molecular Psychiatry*, *21*(6), 749–757. https://doi.org/10.1038/mp.2016.49

Smoller, J. W. (2016). The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. *Neuropsychopharmacology*, *41*(1), 297–319. https://doi.org/10.1038/npp.2015.266

Smoller, J. W. (2020). Anxiety genetics goes genomic. *The American Journal of Psychiatry*, *177*(3), 190–194. https://doi.org/10.1176/appi.ajp.2020.20010038

Smoller, J. W., Andreassen, O. A., Edenberg, H. J., Faraone, S. V., Glatt, S. J., & Kendler, K. S. (2019). Psychiatric genetics and the structure of

psychopathology. *Molecular Psychiatry*, *24*(3), 409–420. https://doi.org/10.1038/s41380-017-0010-4

So, H.-C., Chau, C. K.-L., Chiu, W.-T., Ho, K.-S., Lo, C.-P., Yim, S. H.-Y., & Sham, P.-C. (2017). Analysis of genome-wide association data highlights candidates for drug repositioning in psychiatry. *Nature Neuroscience*, *20*(10), 1342–1349. https://doi.org/10.1038/nn.4618

So, H.-C., Chau, C. K.-L., Lau, A., Wong, S.-Y., & Zhao, K. (2019). Translating GWAS findings into therapies for depression and anxiety disorders: Gene-set analyses reveal enrichment of psychiatric drug classes and implications for drug repositioning. *Psychological Medicine*, *49*(16), 2692–2708. https://doi.org/10.1017/S0033291718003641

Spielberger, C. D. (1985). Anxiety, cognition and affect: A state-trait perspective. In A. H. Tuma, & J. D. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 171–182). New Jersey: Lawrence Erlbaum Associates, Inc.

Stein, M. B., Chen, C.-Y., Jain, S., Jensen, K. P., He, F., Heeringa, S. G., … Army STARRS Collaborators. (2017). Genetic risk variants for social anxiety. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *174*(2), 120–131. https://doi.org/10.1002/ajmg.b.32520

Strawn, J. R., & Levine, A. (2020). Treatment response biomarkers in anxiety disorders: From neuroimaging to neuronally-derived extracellular vesicles and beyond. *Biomarkers in Neuropsychiatry*, *3*, 100024.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, *60*(12), 1187–1192. https://doi.org/10.1001/archpsyc.60.12.1187

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *The American Journal of Psychiatry*, *157*(10), 1552–1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Tam, V., Patel, N., Turcotte, M., Bossé, Y., Paré, G., & Meyre, D. (2019). Benefits and limitations of genome-wide association studies. *Nature Reviews. Genetics*, *20*(8), 467–484. https://doi.org/10.1038/s41576-019-0127-1

Tambs, K., Czajkowsky, N., Røysamb, E., Neale, M. C., Reichborn-Kjennerud, T., Aggen, S. H., … Kendler, K. S. (2009). Structure of genetic and environmental risk factors for dimensional representations of DSM-IV anxiety disorders. *The British Journal of Psychiatry*, *195*(4), 301–307. https://doi.org/10.1192/bjp.bp.108.059485

Trzaskowski, M., Eley, T. C., Davis, O. S. P., Doherty, S. J., Hanscombe, K. B., Meaburn, E. L., … Plomin, R. (2013). First genome-wide association study on anxiety-related behaviours in childhood. *Plos One*, *8*(4), e58676. https://doi.org/10.1371/journal.pone.0058676

Viana, A. G., Beidel, D. C., & Rabian, B. (2009). Selective mutism: A review and integration of the last 15 years. *Clinical Psychology Review*, *29*(1), 57–67. https://doi.org/10.1016/j.cpr.2008.09.009

Visscher, P. M., Wray, N. R., Zhang, Q., Sklar, P., McCarthy, M. I., Brown, M. A., & Yang, J. (2017). 10 Years of GWAS discovery: Biology, function, and translation. *American Journal of Human Genetics*, *101*(1), 5–22. https://doi.org/10.1016/j.ajhg.2017.06.005

Vukasović, T., & Bratko, D. (2015). Heritability of personality: A meta-analysis of behavior genetic studies. *Psychological Bulletin*, *141*(4), 769–785. https://doi.org/10.1037/bul0000017

Walter, S., Glymour, M. M., Koenen, K., Liang, L., Tchetgen Tchetgen, E. J., Cornelis, M., … Kubzansky, L. D. (2013). Performance of polygenic scores for predicting phobic anxiety. *Plos One*, *8*(11), e80326. https://doi.org/10.1371/journal.pone.0080326

Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2014). The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry*, *71*(8), 905–916. https://doi.org/10.1001/jamapsychiatry.2014.655

Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2016). The stability and change of etiological influences on depression, anxiety symptoms and their co-occurrence across adolescence and young adulthood. *Psychological Medicine*, *46*(1), 161–175. https://doi.org/10.1017/S0033291715001634

Watson, D. (2005). Rethinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. *Journal of Abnormal Psychology*, *114*(4), 522–536. https://doi.org/10.1037/0021-843X.114.4.522

Weber, H., Richter, J., Straube, B., Lueken, U., Domschke, K., Schartner, C., … Reif, A. (2016). Allelic variation in CRHR1 predisposes to panic disorder: Evidence for biased fear processing. *Molecular Psychiatry*, *21*(6), 813–822. https://doi.org/10.1038/mp.2015.125

Wigmore, E. M., Hafferty, J. D., Hall, L. S., Howard, D. M., Clarke, T.-K., Fabbri, C., … McIntosh, A. M. (2020). Genome-wide association study of antidepressant treatment resistance in a population-based cohort using health service prescription data and meta-analysis with GENDEP. *The Pharmacogenomics Journal*, *20*(2), 329–341. https://doi.org/10.1038/s41397-019-0067-3

Wray, N. R., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., Murray, G. K., … Visscher, P. M. (2020). From basic science to clinical application of polygenic risk scores: A primer. *JAMA Psychiatry, 78(1), 101-109.* https://doi.org/10.1001/jamapsychiatry.2020.3049

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., & Bybjerg-Grauholm, J. … *et al.*the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, *50*(5), 668–681. https://doi.org/10.1038/s41588-018-0090-3

Young, A. I., Benonisdottir, S., Przeworski, M., & Kong, A. (2019). Deconstructing the sources of genotype-phenotype associations in humans. *Science (New York, N.Y.)*, *365*(6460), 1396–1400. https://doi.org/10.1126/science.aax3710

Zamani, M., Alizadeh-Tabari, S., & Zamani, V. (2019). Systematic review with meta-analysis: The prevalence of anxiety and depression in patients with irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*, *50*(2), 132–143. https://doi.org/10.1111/apt.15325

Zavos, H. M. S., Rijsdijk, F. V., Gregory, A. M., & Eley, T. C. (2010). Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. *Journal of Affective Disorders*, *124*(1–2), 45–53. https://doi.org/10.1016/j.jad.2009.10.030

Zhang, H.-T., Huang, Y., Masood, A., Stolinski, L. R., Li, Y., Zhang, L., … O'Donnell, J. M. (2008). Anxiogenic-like behavioral phenotype of mice deficient in phosphodiesterase 4B (PDE4B). *Neuropsychopharmacology*, *33*(7), 1611–1623. https://doi.org/10.1038/sj.npp.1301537

Zhu, Z., Zheng, Z., Zhang, F., Wu, Y., Trzaskowski, M., Maier, R., … Yang, J. (2018). Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nature Communications*, *9*(1), 224. https://doi.org/10.1038/s41467-017-02317-2

Ziegler, C., Grundner-Culemann, F., Schiele, M. A., Schlosser, P., Kollert, L., Mahr, M., … Domschke, K. (2019). The DNA methylome in panic disorder: A case-control and longitudinal psychotherapy-epigenetic study. *Translational Psychiatry*, *9*(1), 314. https://doi.org/10.1038/s41398-019-0648-6