The World Journal of Biological Psychiatry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iwbp20

Systematic review of genome-wide association studies of anxiety disorders and neuroticism

Kristien van der Walt, Megan Campbell, Dan J. Stein & Shareefa Dalvie

To cite this article: Kristien van der Walt, Megan Campbell, Dan J. Stein & Shareefa Dalvie (2022): Systematic review of genome-wide association studies of anxiety disorders and neuroticism, The World Journal of Biological Psychiatry, DOI: 10.1080/15622975.2022.2099970

To link to this article: https://doi.org/10.1080/15622975.2022.2099970

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
https://doi.org/10.1080/15622975.2022.2099970

ORIGINAL INVESTIGATION

OPEN ACCESS Check for updates

Systematic review of genome-wide association studies of anxiety disorders and neuroticism

Kristien van der Walt[a], Megan Campbell[b,c], Dan J. Stein[d] and Shareefa Dalvie[d,e,f]

[a]Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa; [b]MRC Genomic and Precision Medicine Research Unit, Division of Human Genetics. Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa; [c]Global Initiative for Neuropsychiatric Genetics Education in Research (GINGER) program, Harvard T.H. Chan School of Public Health and the Stanley Center for Psychiatric Research at the Broad Institute of Harvard and MIT, Boston, Massachusetts, USA; [d]SAMRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa; [e]Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; [f]Biomedical Research and Innovation Platform (BRIP), South African Medical Research Council (SAMRC), Cape Town

ABSTRACT

Objectives: To summarise SNP associations identified by genome-wide association studies (GWASs) of anxiety disorders and neuroticism; to appraise the quality of individual studies, and to assess the ancestral diversity of study participants.

Methods: We searched PubMed, Scopus, PsychInfo and PubPsych for GWASs of anxiety disorders, non-diagnostic traits (such as anxiety sensitivity), and neuroticism, and extracted all SNPs that surpassed genome-wide significance. We graded study quality using Q-genie scores and reviewed the ancestral diversity of included participants.

Results: 32 studies met our inclusion criteria. A total of 563 independent significant variants were identified, of which 29 were replicated nominally in independent samples, and 3 were replicated significantly. The studies had good global quality, but many smaller studies were underpowered. Phenotypic heterogeneity for anxiety (and less so for neuroticism) seemed to reflect the complexity of capturing this trait. Ancestral diversity was poor, with 70% of studies including only populations of European ancestry.

Conclusion: The functionality of genes identified by GWASs of anxiety and neuroticism deserves further investigation. Future GWASs should have larger sample sizes, more rigorous phenotyping and include more ancestrally diverse population groups.

ARTICLE HISTORY
Received 14 March 2022
Revised 9 June 2022
Accepted 6 July 2022

KEYWORDS
Anxiety; neuroticism; GWAS; genetics; systematic review

Introduction

Anxiety disorders (ADs) are a group of conditions characterised by excessive and enduring fear, anxiety or avoidance of perceived threats (Craske et al. 2017). This group of disorders, which includes panic disorder (PD), social anxiety disorder, specific phobia and generalised anxiety disorder (GAD), may involve underlying dysregulation of the basic-threat response (Craske et al. 2009). ADs are relatively common with a current prevalence of about 7.3% (Baxter et al. 2013). These disorders are associated with significant distress and can culminate in serious disability. (Craske et al. 2017).

Neuroticism is one of the higher-order domains in the five-factor model of personality and represents individual differences in the tendency towards negative emotions or negative thoughts (Costa and Mccrae 1992; Goldberg 1993). Neuroticism is highly comorbid with ADs clinically (Jylhä and Isometsä 2006), and there is a significant genetic correlation between the risk of ADs and neuroticism (previous studies suggest a genetic correlation of about 0.8) (Hettema et al. 2004; Ohi et al. 2020) with neuroticism possibly representing an "endophenotype" of ADs and other psychiatric disorders (similar evidence exists for the major depressive disorder) (Hettema et al. 2004; Kendler et al. 2006; Wray et al. 2018)).

ADs and neuroticism have a considerable genetic component, with a heritability of between 20 and

CONTACT Shareefa Dalvie shareefa.dalvie@mrc.ac.za South African Medical Research Council, Francie van Zijl Drive, Parow Valley, Cape Town, South Africa, 7501

Supplemental data for this article can be accessed at https://doi.org//10.1080/15622975.2022.2099970.

40%, (Smoller et al. 2009). This genetic contribution is complex, likely involving a large number of genes of a small individual effect, coupled with gene-gene and gene-environment interactions (Smoller et al. 2009). Genome-wide association studies (GWAS) test large numbers of SNPs for association with a given phenotype. GWAS, and more recently meta- and "mega" -analysis of GWAS (in which collaborative groups collate data for joint analysis) is a powerful method for detecting genetic associations for complex traits.

A growing number of GWASs have examined anxiety and anxiety-related traits, such as neuroticism, but these have not been systematically summarised or meta-analysed. Recent articles raise concern over the persistent lack of ancestral diversity in GWAS, which limits the accuracy and broader relevance of findings, and threatens to exacerbate existing healthcare disparities as genomic medicine advances (Need and Goldstein 2009; Popejoy and Fullerton 2016; Peterson et al. 2019).

The aims of this review are to:

1. Summarise SNP associations identified by GWASs of AD and neuroticism, combining results in a meta-analysis, if appropriate.
2. Appraise the quality of individual studies and assess the ancestral diversity of study participants.

Methods

The study protocol for this review was registered with the international prospective register of systematic reviews (PROSPERO protocol CRD42021118062). PRISMA guidelines were used to identify relevant studies for inclusion (Page et al. 2021). We systematically searched PubMed, Scopus, PsychInfo and PubPsych. We also searched Web of Science and WorldCat for grey literature and hand-searched the reference lists of eligible studies for additional reports. All databases were searched up to 2 June 2022. The following search query was used for PubMed and modified appropriately for other databases – no limits were used: *((genome-wide association study OR genome-wide association studies) OR (genome wide association study OR genome wide association studies) OR (GWAS OR GWA study OR GWA studies) OR ("Genome-Wide Association Study"[Mesh]) OR (whole genome association study OR whole genome association studies OR genome wide association scan OR genome wide association scans OR genome wide association analysis OR genome wide association analyses)) AND ((anxiety disorder OR anxiety disorders) OR (anxiety neurosis OR anxiety neuroses OR anxiety neurotic) OR "Anxiety Disorders"[Majr]))*. Given the high comorbidity and genetic overlap between ADs and neuroticism, GWASs of neuroticism were included in this review.

We merged our search results and removed any duplicates. Next, abstracts not mentioning GWAS and either anxiety disorders, anxiety traits, or neuroticism, were removed. Two investigators then independently screened the remaining full-text papers for eligible studies (Figure 1). We included only GWASs of ADs, non-diagnostic traits (such as anxiety sensitivity), and neuroticism. Studies that were conducted exclusively on animals, children under 16 years, not published in English, or where data was only published in abstract form (e.g. meeting or conference abstracts) were excluded. Any disagreements were resolved via discussion and input from a third investigator. We extracted all SNPs that surpassed genome-wide significance ($p < 5 \times 10^{-8}$). Two investigators independently evaluated the risk of bias in each study using Q-genie, a validated tool developed by McMaster University for rating the quality of genetic association studies (Sohani et al. 2016).

Results

Literature search

Our search identified a total of 2665 records and a final 32 met the inclusion criteria (Table 1). All included GWASs were published between 2008 and 2022. Sample sizes ranged from only 56 to over 400,000 participants. Studies published later generally had larger samples sizes, likely due to the emergence of large-scale population-based biobanks and consortia (collaborations between multiple GWAS cohorts) such as the UK Biobank (Okbay et al. 2016; Smith et al. 2016; Lo et al. 2017; Luciano et al. 2018; Nagel et al. 2018; Purves et al. 2019), 23andMe (Lo et al. 2017; Luciano et al. 2018; Nagel et al. 2018) and Genetics of Personality Consortium (Genetics of Personality Consortium 2015; Okbay et al. 2016; Lo et al. 2017; Luciano et al. 2018; Nagel et al. 2018). Genotyping was performed using Illumina, Affymetrix, Perlegen or custom genotyping platforms. The mean age range for all of the studies was between 13 and 81 years.

Studies varied significantly in terms of the phenotype used to capture anxiety. Some studies measured quantitative traits (e.g. anxiety sensitivity) or combined multiple different anxiety disorder cases under one phenotype, assuming a degree of dimensionality to the genetic architecture of anxiety (an underlying

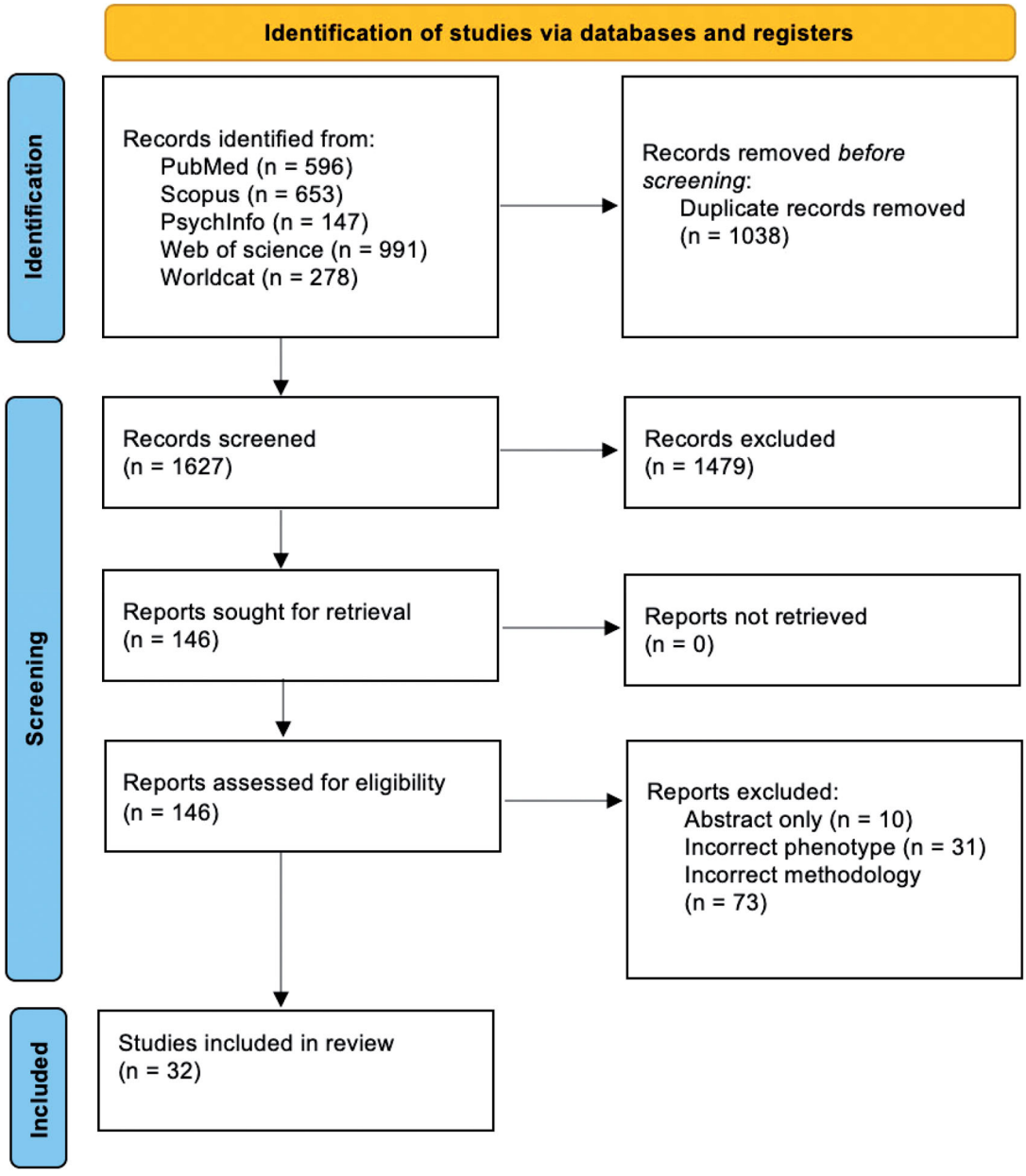

Figure 1. Summary of methodology.

continuum of biological variance, with common features that span multiple categories of anxiety disorder). Other studies took a categorical approach, testing genetic association against diagnoses of specific disorders e.g. panic disorder. We intentionally designed our inclusion criteria to capture both approaches. Diagnoses were based on either DSM-IV (American Psychiatric Association (APA) 2000), DSM-5 (American Psychiatric Association (APA) 2013) or ICD-10 (World Health Organisation (WHO 1992) classification systems. The CIDI (Composite International Diagnostic Interview) (World Health Organisation (WHO 2001) which can be administered by a lay person, was the most commonly used interview tool, either in full (CIDI-SC) or short-form (CIDI-SF). Other tools used were SCID-5 (structured clinical interview for DSM-5) (American Psychiatric Association (APA) 2013), SCAN (schedules for clinical assessment in neuropsychiatry) (WHO 1994), or MINI (mini international neuropsychiatric interview) (Sheehan et al. 1997), which are designed for administration by psychiatrists or psychologists. Other studies used screening tools (e.g. Generalised Anxiety Disorder 2-item or GAD-2) (Spitzer et al. 2006), and self-administered questionnaires (e.g. agoraphobic cognitions questionnaire) (Chambless et al. 1984), or self-report of previous diagnoses. Large-scale consortia went on to combine multiple measures of anxiety using item-

Table 1. Genome-wide association studies for anxiety and neuroticism meet inclusion criteria.

Reference	Study design	Ancestry	Sample size	Phenotype – measurement tool
Shifman et al. 2008	GWAS	European	2054	Neuroticism – Revised EPQR-N Scale (23 items)
van den Oord et al. 2008	GWAS	European	1227	Neuroticism – EPQR-N (12 item version)
Otowa et al. 2009	GWAS	Japanese	400 (200 cases, 200 controls)	Panic disorder – DSM-IV diagnosis via MINI (mini international neuropsychiatric interview) and review of medical records
Calboli et al. 2010	GWAS	European	2239	Neuroticism – EPQ-N
Terracciano et al. 2010	GWAS	European	3972	Neuroticism – NEO-PI-R, administered by trained psychologists
Aragam et al. 2013	GWAS	European	2748	Quantitative neuroticism score based on NEO 5 Factor Personality Index (NEO-FFI)
de Moor et al. 2015	GWAS	European	17375	Neuroticism – NEO-FFI or NEO-PIR
Erhardt et al. 2011	GWAS	European	438 (216 cases, 222 controls)	Panic disorder – DSM IV diagnosis by trained psychiatrist using SKID-1 and SKID-2 (structured clinical interviews for DSM IV)
Gregersen et al. 2012	GWAS	European	56 (13 cases, 43 controls)	Panic disorder – ICD-10 diagnosis as per "present state examination"
Luciano et al. 2012	GWAS and meta-analysis	European	6268	Neuroticism – EPQR-N (short form), International Personality Item Pool Big-Five 50-item inventory
Otowa et al. 2012	GWAS and meta-analysis	Japanese	2435 (718 cases, 1717 controls)	Panic disorder – DSM-IV diagnosis confirmed by MINI (mini international neuropsychiatric interview) and review of medical records
Kim et al. 2013	GWAS	Korean	1089	Neuroticism – NEO-PI-R (neuroticism scale), Korean short version, 18 items
Schosser et al. 2013	GWAS	European	3110	Anxiety in MDD – Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview.
Otowa et al. 2014	GWAS	European, African American	1697 EA, 597 AA (case-control GWAS); 2540 EA, 849 AA (factor score GWAS)	Anxiety disorders – CIDI-SF with DSM-based algorithms (GAD, panic attacks, agoraphobia, social phobia, specific phobia) – (1) cases (2) factor analysis-derived continuous score
Davies et al. 2015	GWAS	Not reported (Twins UK registry)	730	Anxiety sensitivity – Anxiety Sensitivity Index (16 item)
de Moor et al. 2015	Meta-analysis	European	63661	Neuroticism – Item response theory used to combine multiple measurement tools
Okbay et al. 2016	GWAS and meta-analysis	European	170910 (neuroticism cohort)	Neuroticism – EPQ-N (12 item version) in UK biobank, EPQ/NEO/international personality item pool inventory in GPC
Otowa et al. 2016	Meta-analysis	European	18186 (factor score GWAS), 17310 (case-control GWAS)	Anxiety disorders (GAD, PD, agoraphobia, social phobia, specific phobia) – various measurement instruments, DSM-based, (1) case-control (2) quantitative phenotype factor scores
Smith et al. 2016	GWAS and meta-analysis	European	91370 (UK biobank GWAS), 106716 (meta-analysis)	Neuroticism – EPQ-R-S (short form)
Deckert et al. 2017	GWAS	European	1370	Agoraphobia – ACQ (agoraphobic cognitions questionnaire)
Dunn et al. 2017	GWAS	Hispanic	12282	Generalised Anxiety disorder – Spielberger Trait Anxiety inventory – short-form – reponses used to create GAD symptoms score based on 3 DSM-V criteria
Kim et al. 2017	GWAS and meta-analysis	Korean	5584	Facets of Neuroticism – Revised NEO PI-R
Lo et al. 2017	GWAS and meta-analysis	European	122867	Neuroticism – in 23andme sample: Big Five Inventory (44 questions) in GPC-1 sample: NEO-FFI; in GPC-2 sample: harmonisation of multiple measures using item response theory
Stein et al. 2017	GWAS and meta-analysis	European, African American, Latino	11268 (EUR cohort), 2622 (AFR cohort), 3438 (LAT cohort)	Social Anxiety — 5 survey items in the CIDI-SC

(*continued*)

Table 1. Continued.

Reference	Study design	Ancestry	Sample size	Phenotype – measurement tool
Nagel et al. 2018	Meta-analysis	European	449484	Neuroticism – EPQ-RS, Big5 personality summary score, NEO-FFI in UK biobank, 23andme and GPC samples respectively
Luciano et al. 2018	GWAS and meta-analysis	European	329821	Neuroticism – EPQN (12 item version)
Hettema et al. 2020	GWAS and meta-analysis	European, Latino, African American	16510 (STARRS meta-analysis), 28950 (EUR STARRS + ANGST meta-analysis), 34696 (full STARRS + ANGST meta-analysis)	Anxiety disorders (GAD, panic disorder, phobias) – CIDI-SC answer items used as proxy for lifetime GAD and panic disorder, and phobias using screening items and clinical information.
Meier et al. 2019	GWAS	European	31880 (12655 cases, 19225 controls)	Anxiety and stress-related diagnoses – ICD-10 diagnosis by psychiatrist
Purves et al. 2019	GWAS	European	83566 (25453 cases, 58113 controls) – lifetime anxiety disorder GWAS, 77124 (19 012 cases, 58 113 controls) – current anxiety GWAS	Anxiety – (1) Lifetime anxiety disorder (self-report, clinician-provided or probable using DSM IV/CIDI) (2) Current Anxiety Symptoms: GAD-7 with >/= 10/21
Baselmans et al. 2019	Meta-analysis	European	582989 (neuroticism meta-analysis)	Neuroticism – meta-analysis of 4 studies (see Brice et al. 1993; Okbay et al. 2016; Bycroft et al. 2017; Lo et al. 2017)
Levey et al. 2020	GWAS and meta-analysis	European and African American	199611 (GAD-2 GWAS), 224330 (self-report of physician diagnosis GWAS)	Anxiety – GAD-2 (2 items) and self-report of physician diagnosis
Forstner et al. 2021	GWAS and meta-analysis	European	10240 (2248 cases, 7992 controls)	Panic disorder – Lifetime diagnosis (DSM III-R, DSM IV or ICD-10 criteria)

response theory. Neuroticism was measured in a more standardised fashion: most studies used either the revised EPQR-N (Eysenck Personality Questionnaire – Neuroticism) scale (Eysenck and Eysenck 1975), the revised NEO personality inventory (or five-factor index) (Costa and Mccrae 1992), a shorter version or the Big Five inventory (John et al. 2008).

Quality assessment

Nearly all (29/32) studies met Q-genie score standards for good global quality (scores of over 45 for those with control groups, and over 40 for those without). Two studies were of moderate quality (scoring 42 and 45), and no studies were of poor quality. Notably, while the studies had good global quality, many scored poorly (<2/7) on two subsections: "sample size and power" (3/32) and "selection and definition of the outcome of interest" (10/32). A table of the Q-genie scores for each study can be found in Table S1.

Diversity assessment

Most studies included populations of European descent (23 of 32 studies (72%)), with the exception of 5 studies that included Hispanic, Latin American and/or African American cohorts, 2 studies of Korean populations, and 2 studies of Japanese populations. Compared to earlier studies, later studies had improved representation of non-European populations (only 18% included populations of non-European ancestry before 2013, and 38% thereafter).

Genome-wide significant SNPs for anxiety

Nine studies identified SNPs significantly associated with anxiety at the genome-wide level in the discovery cohorts (Table 2). While none of the SNPs listed in Table 2 were significantly associated with anxiety (at genome-wide threshold $p < 5 \times 10^{-8}$) in replication cohorts, 7 SNPs were replicated at 'nominal' association levels ($p < 5 \times 10^{-3}$). These include two variants (rs78726293 and rs191260602) in *GLRB* (glycine receptor subunit beta) that were associated with agoraphobia (Deckert et al. 2017), two variants associated with a 'lifetime anxiety' phenotype – one in an intergenic region (rs10959883), and another (rs3807866) in the gene *TMEM106B* (Transmembrane Protein 106B) (Purves et al. 2019), and three variants associated with a generalised anxiety phenotype – located in the genes *SATB1-AS1* (SATB1 Antisense RNA 1) (rs4390955), *ESR1* (Oestrogen receptor 1) (rs6557168), and near the long noncoding RNA *LINC01360* and *LRRIQ3* (rs12023347) (Levey et al. 2020). One SNP, rs1067327, located in an intronic region of *CAMKMT*, was associated with anxiety in both the Otowa et al. (2016) GWAS (Otowa et al. 2016), and the Hettema meta-analysis ($p < 5 \times 10^{-8}$) (Hettema et al. 2020). This is unsurprising given that these studies had overlapping samples. Using gene-set enrichment analysis, Otowa

Table 2. SNPs are significantly associated with anxiety at the genome-wide level.

Study	Phenotype	Subgroup (if relevant)[a]	Variant	Chr	*P* value	Location	Gene
Otowa et al. 2009	Panic disorder	NA	rs860554	1	4.60×10^{-8}	Intronic	*PKP1*
			rs12579350	12	3.73×10^{-9}	Intronic	*TMEM16B*
Davies et al. 2015	Anxiety sensitivity	NA	rs13334105	16	4.39×10^{-8}	Exonic	*RBFOX1 gene*
Otowa et al. 2016	Anxiety disorders (GAD, PD, agoraphobia, social phobia, specific phobia)	*Case-control*	rs1709393	3	1.65×10^{-8}	Intronic	*LOC152225*
		Factor score	rs1067327	2	2.86×10^{-9}	Exonic	*CAMKMT*
Stein et al. 2017	Social anxiety	*African American*	rs78924501	1	3.58×10^{-8}	Intronic	Downstream from *CCBL2/ KYAT3*
		European	rs708012	6	1.55×10^{-8}	3′ UTR	–
Deckert et al. 2017	Agoraphobia	NA	rs78726293	4	3.3×10^{-8}	Intronic	*GLRB*
			rs191260602	2	3.9×10^{-8}	Intronic	*GLRB*
Dunn et al. 2017	Generalised anxiety disorder	NA	rs78602344	6	4.18×10^{-8}	Intronic	*THBS2*
Purves et al. 2019	Anxiety disorders	*Lifetime anxiety*	rs10959883	9	2.9×10^{-11}	intergenic	–
			rs1187280	9	6.6×10^{-9}	Intron	*NTRK2*
			rs4855559	3	3.7×10^{-8}	Intron	Myosin Heavy Chain 15
			rs2861139	5	2.6×10^{-9}	Intergenic	–
			rs3807866	7	4.8×10^{-8}	5′ upstream	*TMEM106B*
		Current anxiety	rs17189482	9	4.2×10^{-9}	Intergenic	–
Hettema et al. 2020	Anxiety disorders (GAD, panic disorder, phobias)	*ANGST + EUR STARRS*	rs1067327	–	2.15×10^{-10}	Intronic	*CAMKMT*
			rs1067394	–	9.08×10^{-11}	Intronic	*CAMKMT*
Levey et al. 2020[b]	Generalised anxiety	*GAD-2 score,* EA	rs4603973	3	6.18×10^{-11}	Intronic	*SATB1-AS1*
			rs4390955	3	7.78×10^{-11}	Intronic	*SATB1-AS1*
			rs6557168	6	1.33×10^{-9}	Intronic	*ESR1*
			rs12023347	1	8.88×10^{-9}	Intergenic	Near long noncoding RNA *LINC01360* and *LRRIQ3*
			rs56226325	7	2.01×10^{-8}	Intronic	*MAD1L1*
			rs6090040	20	3.28×10^{-8}	Intronic	In and around *TCEA2, RGS19* and *OPRL1* genes
		GAD-2 score, AA	rs575403075	7	2.82×10^{-8}	Intergenic	Near *TRPV6*
		Case-control score, EA	rs35546597	17	1.88×10^{-8}	Intergenic	Near *AURKB*
			rs10534613	7	4.92×10^{-8}	Intron	*IQCE*

[a]For studies where significant SNPs were identified in GWASs conducted in separate samples based on either population group or phenotype measure.
[b]Chr: chromosome*; PKP1:* Plakophilin 1; *TMEM16B*: transmembrane protein 16B*; RBFOX1:* RNA binding fox-1 homolog 1; GAD: Generalised Anxiety disorder; PD: panic disorder; *CAMKMT:* Calmodulin-Lysine N-Methyltransferase; *KYAT-3:* Kynurenine Aminotransferase 3; *GLRB:* Glycine Receptor Beta; *THBS2:* thrombospondin 2; *NTRK2:* Neurotrophic Receptor Tyrosine Kinase 2; *TMEM106B:* Transmembrane protein 106B; ANGST + EUR STARSS: Anxiety Neurogenetics Study + European Study to Assess Risk and Resilience in service members; GAD-2: Generalised anxiety disorder 2-item; EA: European American; AA: African American; *SATB1-AS1:* SATB1 Antisense RNA 1; *ESR1:* Oestrogen Receptor 1; *LINC01360:* Long Intergenic Non-Protein Coding RNA 1360; *LRRIQ3*: Leucine Rich Repeats And IQ Motif Containing 3; *MAD1L1:* Mitotic Arrest Deficient 1 Like 1; *TCEA2:* Transcription elongation factor A protein 2; *RGS19*: Regulator Of G Protein Signalling 19; *OPRL1:* Opioid Related Nociceptin Receptor 1; *TRPV6*: Transient Receptor Potential Cation Channel Subfamily V Member 6; *AURKB:* Aurora Kinase B; *IQCE*: IQ Motif Containing E.

et al. (2014) found significant associations between anxiety disorders and four gene-ontology (GO) terms ('*pattern specification process*', '*cytokine binding*', '*nucleoplasm*' and '*transcription regulator activity*' (Table S2) (Otowa et al. 2014). However, these were not tested in replication cohorts.

Genome-wide significant SNPs for neuroticism

A total of 12 GWASs and 8 meta-analyses have been conducted for neuroticism, identifying 540 independent genome-wide significant loci (Table S3). Of the over 14,000 total significant SNPs identified, 5850 significant SNPs were reported in more than one study, which is unsurprising given the considerable sample overlap, with most studies drawing from one or more of three major consortia: the UK Biobank, Genetics of Personality Consortium and 23andme (Table S4). SNPs reported in more than two studies are available in our supplementary materials (Table S4).

Only three of the GWASs reviewed here included replication cohorts in their study (Genetics of Personality Consortium 2015; Lo et al. 2017; Luciano et al. 2018). From these, three SNPS (rs6981523 (Lo et al. 2017), rs2953805 and rs6982308 (Luciano et al. 2018)) were replicated at the genome-wide level, and 21 SNPs were replicated at a nominally significant level ($p < 0.05$) (Table S5).

The variant rs6981523 is located on chromosome 8p23.1, a region containing a well-known inversion polymorphism. This SNP was found to be significant in both the 23andme/Genetics of Personality Consortium

(Lo et al. 2017) and UK Biobank (Luciano et al. 2018) studies, as well as a 2019 meta-analysis of 4 studies (Baselmans et al. 2019).

Notably, excepting the 23andme/GPC meta-analysis ($n = 112867$) (Lo et al. 2017), which included a large sample from the UK biobank ($n = 91370$) for replication analysis, replication samples were far smaller than their discovery samples. They were thus unlikely to confirm SNP associations for neuroticism, given the small effect sizes of these associations.

Two studies identified significant associations between neuroticism and gene ontology terms or pathways, and one between neuroticism 'facets' and gene ontology terms (Table S2). No pathways were tested in replication cohorts. Gene set analysis implicated '*neurogenesis*' and '*neuron differentiation*' with neuroticism in two overlapping samples: a combined sample from the UK Biobank, Genetics of Personality Consortium and 23andme ($p = 4.43 \times 10^{-9}$ and 3.12×10^{-8}, respectively (Nagel et al. 2018)), as well as in a large UK Biobank sample (p values of 5.35×10^{-7} and 2.36×10^{-7}(Genetics of Personality Consortium 2015), respectively).

Discussion

In this review of GWASs of anxiety and neuroticism, the main findings were 1) a total of 26 variants were identified for ADs, of which 7 were replicated nominally, but none were replicated significantly, 2) a total of 540 independent variants were identified for neuroticism, of which 21 were replicated nominally, and 3 were replicated significantly 3) the studies had good global quality, but many smaller studies were underpowered and ancestral diversity was poor, with 72% of studies including only populations of European ancestry.

The variants significantly associated with anxiety were two non-coding SNPs, rs78726293 and rs191260602, located in *GLRB*. These variants were specifically associated with 'agoraphobic cognitions' (an anxiety phenotype based on the Agoraphobic Cognitions Questionnaire (Chambless et al. 1984)) and replicated at nominal association levels in a larger sample (Deckert et al. 2017). Rare *GLRB* mutations have been previously associated with hyperekplexia – a neurological disorder characterised by an exaggerated startle reaction and agoraphobic behaviour (Al-Owain et al. 2012). In a post-GWAS analysis, healthy volunteers carrying *GLRB* risk alleles showed increased startle reactivity and impaired startle habituation in a startle reflex paradigm. These *GLRB*-carrying individuals also showed increased activation of the fear network on fMRI and increased skin conductance in response to conditioned stimuli. The authors postulated increased startle responses as a basic mechanism underlying defensive reactivity (responding negatively to threats) in agoraphobic behaviour (Deckert et al. 2017). In addition, partial *GLRB* knockout resulted in agoraphobic behaviour in a mouse model (Deckert et al. 2017).

A variant (rs3807866) in the gene *TMEM106B* was significantly associated and nominally replicated with lifetime anxiety (Purves et al. 2019). Increased expression of TMEM106B has been associated with lysosomal enlargement and cell toxicity, which plausibly mediates fear learning via neurotoxicity, a link which has been demonstrated in mice (Jing et al. 2015). It has also previously been associated with depression, which is highly comorbid with anxiety and likely shares some genetic overlap with this disorder (Waszczuk et al. 2014; Wray et al. 2018; Purves et al. 2019).

A GWAS of GAD-2 scores in a large European American population found significantly associated variants in and around *SATB1* and the antisense gene *SATB-AS1*, which were replicated at nominal association levels in an independent sample (Levey et al. 2020). *SATB1* is a global regulator influencing multiple genes involved in neuronal development including corticotropin releasing hormone (CRH), which modulates our stress response via the HPA axis (Balamotis et al. 2012). In the same study, significantly associated variants were identified near *ESR1* and were replicated at nominal association levels. *ESR-1* encodes the ESR1 receptor, an intracellular receptor that is activated by the sex hormone oestrogen. This receptor has been studied extensively in rodents, where it appears to modulate an anxiogenic affect (Borrow and Handa 2017).

Several significant variants were identified near the *LINC01360* and *LRRIQ3* loci and were replicated in a major depressive disorder (MDD) cohort (Levey et al. 2020). As with *TMEM106B,* this finding may speak to the high co-morbidity rates and shared genetic influences between anxiety and depression (Waszczuk et al. 2014). *LINCO1360* is a long non-coding (RNA) that is likely to have a role in the pathogenesis of MDD as shown in a recent study of *Alu* insertion polymorphisms at nearby genetic risk loci, that reduce the genetic risk of MDD and increase expression of this RNA (Liu et al. 2020). *LINCO1360* is preferably expressed in testis, and its mechanistic link to MDD or anxiety is unclear (Liu et al. 2020). *LRRIQ3* encodes a

protein containing a leucine-rich repeat (LRR) domain, and IQ motif protein 3, which is a component of calcium channels and is likely involved in cell-cell communication (Bella et al. 2008). Variants in the region of *LRRIQ3* have been previously associated with chronic pain (Johnston et al. 2019), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), neurodevelopmental disorders (Reuter et al. 2017), and migraine (Gormley et al. 2016). How these variants may functionally relate to anxiety and to these neurological psychiatric disorders, has yet to be explored.

A variant in the *CAMKMT* gene was associated with anxiety in two meta-analyses with overlapping samples (Otowa et al. 2016; Hettema et al. 2020). *CAMKMT* codes for an enzyme (a class I protein methyltransferase) that is involved in the formation of trimethyllysine, an amino acid in calmodulin, which is involved in calcium-dependent signalling (Magnani et al. 2010). Mice with mutant forms of this gene have demonstrated deficits in motor learning, complex coordination, and interestingly, learning of aversive stimuli, implicating CaM methylation as a likely required step in fear learning (Haziza et al. 2015). Differential fear learning behaviours or fear conditioning responses are associated with an increased risk of anxiety disorders (Duits et al. 2015).

Several interesting candidate genes were identified for neuroticism. The variant rs2953805, located in the gene *U3*, which was significantly associated with neuroticism in the UK biobank and replicated in an independent sample, has previously been associated with the morning chronotype (Hu et al. 2016). The morning chronotype or 'morningness' trait is associated with lower neuroticism scores, likely due to a common biological basis as well as a dynamic bidirectional feedback loop: individuals that are more neurotic are likely to have poorer sleep secondary to higher stress levels and lower emotional regulation. As a result of this, poor sleep patterns disrupt emotional regulation which in turn increases levels of neuroticism (Duggan et al. 2014). Another variant, which was significantly associated with neuroticism in the UK biobank, and replicated in an independent sample, is located in the *MRSA* gene (Luciano et al. 2018). This gene codes an antioxidant enzyme implicated in protection against oxidative stress and protein maintenance and has previously been associated with schizophrenia (Walss-Bass et al. 2009). Three meta-analyses reported significantly associated SNPs spanning an inversion polymorphism on chromosome 17 (Okbay et al. 2016; Smith et al. 2016; Nagel et al. 2018). Several candidate genes span this region: *CRHR1* (corticotropin-releasing hormone receptor 1) triggers the downstream release of the hormone cortisol in the presence of CRH, thus playing an important role in the body's stress response. *CHRHR1* has previously been shown to play a role in anxiety-related behaviours in mice and has been genetically associated with panic disorder in humans (Weber et al. 2016). Another gene in this region is *MAPT*, which encodes microtubule-associated protein Tau. Tau is present in the post-synaptic compartments of many neurons (Ittner et al. 2010) and *MAPT* knockout in mice leads to defects in hippocampal long-term depression, as well as mild network-level alterations in brain function (Cantero et al. 2011; Kimura et al. 2014). ; Another variant, located in a well-known inversion polymorphism on chromosome 8 (rs6981523), was significantly associated with neuroticism in a large European sample and replicated at nominal association levels in the UK Biobank (Genetics of Personality Consortium 2015). Significantly associated SNPs in this region were also reported in three additional meta-analyses. The region houses multiple genes related to innate immunity and the nervous system and may be involved in susceptibility to cancer and developmental neuropsychiatric disorders (Tabarés-Seisdedos and Rubenstein 2009). The nearest gene to rs6981523 is *XKR6*, which was also significantly associated with neuroticism in a gene-based analysis of neuroticism in the UK Biobank, and has previously been associated with schizophrenia (Walss-Bass et al. 2009; Luciano et al. 2018). Finally, the pathways '*neurogenesis*' and '*neuron differentiation*' were significantly associated with neuroticism in two large samples (Luciano et al. 2018; Nagel et al. 2018). Reduction in adult neurogenesis has previously been proposed as a mechanism for depression and to a lesser extent, anxiety (Lucassen et al. 2015).

While the global quality of our included studies was good, studies tended to score poorly on specific sections of the Q-genie score. For example, many of the smaller studies were underpowered. Small sample sizes in the GWAS context greatly increase the chances of type II error, especially when studying complex disorders like anxiety, where each genetic association is likely to be of a small overall effect size. This may explain why only 17 of the 32 included studies reported significant findings. While the newer studies in this review, which were able to draw from large databases such as the Psychiatric Genomics Consortium and the UK Biobank, had more success, gaining a full picture is likely to require even larger sample sizes, possibly in the millions (Smoller 2020).

The studies also generally had poorly defined and heterogenous phenotypes, which may obscure the meaningfulness of significantly associated variants. Defining and measuring phenotypes for anxiety poses significant challenges from a genetic perspective. The clinical criteria for anxiety disorders have changed over time, and the boundary between normal and pathological anxiety is unclear. The likely picture is of a large common underlying genetic susceptibility that expresses itself across diagnostic boundaries, in combination with smaller groups of genes that contribute to specific disorders e.g. agoraphobia (Smoller 2020). Genetic susceptibility to anxiety can thus be studied by looking either for anxiety-related traits (e.g. anxiety sensitivity), specific disorders, or ADs generally. In addition, there is a multitude of tools of varying rigour that can be used to measure these traits and disorders. As seen in this review, some of the larger studies of anxiety and neuroticism have sacrificed rigorous phenotyping to gain sample size. Notably, phenotype definitions were generally much more homogenous in studies on neuroticism than on anxiety. This is likely because only a few standardised questionnaires exist for measuring personality, and these self-report tools are regarded as more or less the gold standard.

With a few exceptions, most of the reviewed studies only included European populations, limiting the generalisability and scope of the findings (Otowa et al. 2009; Kim et al. 2013; Otowa et al. 2014; Dunn et al. 2017; Stein et al. 2017; Hettema et al. 2020; Levey et al. 2020). This reflects global trends in genomic research. Nevertheless, several significant SNPs associated with anxiety/neuroticism were identified in populations of diverse ancestry, including rs860554 and rs12579350 in a Japanese sample (Otowa et al. 2009), rs78924501 (Stein et al. 2017) and rs575403075 (Levey et al. 2020) in African American samples, rs78602344 (Dunn et al. 2017) in a Hispanic sample, and rs136001 in a Korean sample (Kim et al. 2017), although none were replicated in independent datasets. Recent initiatives are now starting to collect genetic data for African and Latin American participants with psychiatric disorders (Stevenson et al. 2019; Gulsuner et al. 2020; Camarena et al. 2021).

Our systematic review has several limitations. First, we only included studies published in English and those that were publicly available, and so cannot exclude publication bias. We attempted to limit this bias by searching the grey literature. Secondly, we were unable to combine any results in meta-analysis due to substantial heterogeneity between studies, as well as overlapping samples, and limited access to results from some of the GWASs. However, we have presented a comprehensive list of variants we think is important for follow-up. We recommend that future studies should perform integrative analyses to further explore the functionality of the identified variants, such as in the recent TWAS (transcriptome-wide association analyses) of anxiety traits (Su et al. 2021).

Many of the genetic regions identified present new biological candidates that may improve our understanding of anxiety pathophysiology. Future GWASs of anxiety should have larger sample sizes, more rigorous phenotyping and should include ancestrally diverse population groups. Further, the functionality of the identified variants needs to be investigated.

Acknowledgements

None.

Statement of interest

No potential conflict of interest was reported by the author(s).

ORCID

Megan Campbell http://orcid.org/0000-0001-9481-3747
Dan J. Stein http://orcid.org/0000-0001-7218-7810
Shareefa Dalvie http://orcid.org/0000-0003-2333-4823

References

Al-Owain M, Colak D, Al-Bakheet A, Al-Hashmi N, Shuaib T, Al-Hemidan A, Aldhalaan H, Rahbeeni Z, Al-Sayed M, Al-Younes B, et al. 2012. Novel mutation in GLRB in a large family with hereditary hyperekplexia. Clin Genet. 81(5): 479–484.

American Psychiatric Association (APA) 2000. Diagnostic and statistical manual of mental disorders. Fourth. Washington, DC.

American Psychiatric Association (APA) 2013. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC.

Aragam N, Wang K-S, Anderson JL, Liu X. 2013. TMPRSS9 and GRIN2B are associated with neuroticism: a genome-wide association study in a European sample. J Mol Neurosci. 50(2):250–256.

Balamotis MA, Tamberg N, Woo YJ, 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. Mol Cell Biol. 32(2):333–347.

Baselmans BML, Jansen R, Ip HF, van Dongen J, Abdellaoui A, van de Weijer MP, Bao Y, Smart M, Kumari M, Willemsen G, et al. 2019. Multivariate genome-wide analyses of the well-being spectrum. Nat Genet. 51(3):445–451.

Baxter AJ, Scott KM, Vos T, Whiteford HA. 2013. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 43(5):897–910.

Bella J, Hindle KL, McEwan PA, Lovell SC. 2008. The leucine-rich repeat structure. Cell Mol Life Sci. 65(15):2307–2333.

Borrow AP, Handa RJ. 2017. Estrogen receptors modulation of anxiety-like behavior. Vitam Horm. 103:27–52.

Brice J, Buck N, Prentice-Lane, E eds. 1993. British household panel survey user manual. Colchester: University of Essex.

Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. 2017. Genome-wide genetic data on ~500,000 UK Biobank participants. bioRxiv:166298. Available from: http://biorxiv.org/content/early/2017/07/20/166298.abstract.

Calboli FCF, Tozzi F, Galwey NW, Antoniades A, Mooser V, Preisig M, Vollenweider P, Waterworth D, Waeber G, Johnson MR, et al. 2010. A genome-wide association study of neuroticism in a population-based sample. PLOS One. 5(7):e11504–e11504.

Camarena B, Atkinson EG, Baker M, Becerra-Palars C, Chibnik LB, Escamilla-Orozco R, Jiménez-Pavón J, Koenig Z, Márquez-Luna C, Martin AR, et al. 2021. Neuropsychiatric genetics of psychosis in the Mexican population: a genome-wide association study protocol for schizophrenia, schizoaffective, and bipolar disorder patients and controls. Complex Psychiatry. 7(3–4):60–70.

Cantero JL, Moreno-Lopez B, Portillo F, Rubio A, Hita-Yañez E, Avila J. 2011. Role of tau protein on neocortical and hippocampal oscillatory patterns. Hippocampus. 21(8): 827–834.

Chambless DL, Caputo GC, Bright P, Gallagher R. 1984. Assessment of fear of fear in agoraphobics: the body sensations questionnaire and the agoraphobic cognitions questionnaire. J Consult Clin Psychol. 52(6):1090–1097.

Costa P, Mccrae R. 1992. Neo PI-R professional manual. Psychol Assess Resour. 396:223–256.

Costa PT, McCrae RR. 1992. Four ways five factors are basic. Pers Individ Dif. 13(6):653–665.

Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. 2009. What is an anxiety disorder? Depress Anxiety. 26(12):1066–1085.

Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, Wittchen H-U. 2017. Anxiety disorders. Nat Rev Dis Primers. 3:17024.

Davies MN, Verdi S, Burri A, Trzaskowski M, Lee M, Hettema JM, Jansen R, Boomsma DI, Spector TD. 2015. Generalised anxiety disorder – a twin study of genetic architecture, genome-wide association and differential gene expression. PLOS One. 10(8):e0134865.

Deckert J, Weber H, Villmann C, Lonsdorf TB, Richter J, Andreatta M, Arias-Vasquez A, Hommers L, Kent L, Schartner C, et al. 2017. GLRB allelic variation associated with agoraphobic cognitions, increased startle response and fear network activation: a potential neurogenetic pathway to panic disorder. Mol Psychiatry. 22(10): 1431–1439.

Duggan KA, Friedman HS, McDevitt EA, Mednick SC. 2014. Personality and healthy sleep: the importance of conscientiousness and neuroticism. PLOS One. 9(3):e90628.

Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, van den Hout MA, Baas JMP. 2015. Updated meta-analysis of classical fear conditioning in the anxiety disorders. Depress Anxiety. 32(4):239–253.

Dunn EC, Sofer T, Gallo LC, Gogarten SM, Kerr KF, Chen C-Y, Stein MB, Ursano RJ, Guo X, Jia Y, et al. 2017. Genome-wide association study of generalized anxiety symptoms in the Hispanic Community Health Study/Study of Latinos. Am J Med Genet B Neuropsychiatr Genet. 174(2):132–143.

Erhardt A, Czibere L, Roeske D, Lucae S, Unschuld PG, Ripke S, Specht M, Kohli MA, Kloiber S, Ising M, et al. 2011. TMEM132D, a new candidate for anxiety phenotypes: evidence from human and mouse studies. Mol Psychiatry. 16(6):647–663.

Eysenck HJ, Eysenck S. 1975. Manual of the Eysenck personality questionnaire. London: Hodder and Stoughton

Forstner AJ, Awasthi S, Wolf C, Maron E, Erhardt A, Czamara D, Eriksson E, Lavebratt C, Allgulander C, Friedrich N, et al. 2021. Genome-wide association study of panic disorder reveals genetic overlap with neuroticism and depression. Mol Psychiatry. 26(8):4179–4190.

Genetics of Personality Consortium. 2015. Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depressive disorder. JAMA Psychiatry. 72:642–650.

Goldberg LR. 1993. The structure of phenotypic personality traits. Am Psychol. 48(1):26–34.

Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, Farh K-H, Cuenca-Leon E, Muona M, Furlotte NA, et al. 2016. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 48(8):856–866.

Gregersen N, Dahl HA, Buttenschøn HN, Nyegaard M, Hedemand A, Als TD, Wang AG, Joensen S, Woldbye DP, Koefoed P, et al. 2012. A genome-wide study of panic disorder suggests the amiloride-sensitive cation channel 1 as a candidate gene. Eur J Hum Genet. 20(1):84–90.

Gulsuner S, Stein DJ, Susser ES, Sibeko G, Pretorius A, Walsh T, Majara L, Mndini MM, Mqulwana SG, Ntola OA, et al. 2020. Genetics of schizophrenia in the South African Xhosa. Science. 367(6477):569–573.

Haziza S, Magnani R, Lan D, Keinan O, Saada A, Hershkovitz E, Yanay N, Cohen Y, Nevo Y, Houtz RL, et al. 2015. Calmodulin methyltransferase is required for growth, muscle strength, somatosensory development and brain function. PLOS Genet. 11(8):e1005388.

Hettema JM, Prescott CA, Kendler KS. 2004. Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. Am J Psychiatry. 161(9): 1581–1587.

Hettema JM, Verhulst B, Chatzinakos C, Bacanu S-A, Chen C-Y, Ursano RJ, Kessler RC, Gelernter J, Smoller JW, He F, et al. 2020. Genome-wide association study of shared liability to anxiety disorders in Army STARRS. Am J Med Genet B Neuropsychiatr Genet. 183(4):197–207.

Hu Y, Shmygelska A, Tran D, Eriksson N, Tung JY, Hinds DA. 2016. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. Nat Commun. 7:10448.

Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wölfing H, Chieng BC, Christie MJ, Napier IA, et al. 2010. Dendritic function of tau mediates amyloid-β toxicity in Alzheimer's disease mouse models. Cell. 142(3):387–397.

Jing H, Hao Y, Bi Q, Zhang J, Yang P. 2015. Intra-amygdala microinjection of TNF-α impairs the auditory fear

conditioning of rats via glutamate toxicity. Neurosci Res. 91:34–40.
John OP, Naumann LP, Soto CJ. 2008. Paradigm shift to the integrative Big Five trait taxonomy: history, measurement, and conceptual issues. In: Handbook of personality: theory and research, 3rd ed. New York, NY, US: The Guilford Press. p. 114–158.
Johnston KJA, Adams MJ, Nicholl BI, Ward J, Strawbridge RJ, McIntosh AM, Smith DJ, Bailey MES. 2019. Identification of novel common variants associated with chronic pain using conditional false discovery rate analysis with major depressive disorder and assessment of pleiotropic effects of LRFN5. Transl Psychiatry. 9(1):310.
Jylhä P, Isometsä E. 2006. The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. Depress Anxiety. 23(5):281–289.
Kendler KS, Gatz M, Gardner CO, Pedersen NL. 2006. Personality and major depression: a Swedish longitudinal, population-based twin study. Arch Gen Psychiatry. 63(10): 1113–1120.
Kim H-N, Roh S-J, Sung YA, Chung HW, Lee J-Y, Cho J, Shin H, Kim H-L. 2013. Genome-wide association study of the five-factor model of personality in young Korean women. J Hum Genet. 58(10):667–674.
Kim SE, Kim H-N, Yun Y-J, Heo SG, Cho J, Kwon M-J, Chang Y, Ryu S, Shin H, Shin C, et al. 2017. Meta-analysis of genome-wide SNP- and pathway-based associations for facets of neuroticism. J Hum Genet. 62(10):903–909.
Kimura T, Whitcomb DJ, Jo J, Regan P, Piers T, Heo S, Brown C, Hashikawa T, Murayama M, Seok H, et al. 2014. Microtubule-associated protein tau is essential for long-term depression in the hippocampus. Philos Trans R Soc Lond B Biol Sci. 369(1633):20130144.
Levey DF, Gelernter J, Polimanti R, Zhou H, Cheng Z, Aslan M, Quaden R, Concato J, Radhakrishnan K, Bryois J, et al. 2020. Reproducible genetic risk loci for anxiety: results from ∼200,000 participants in the million veteran program. Am J Psychiatry. 177(3):223–232.
Liu W, Li W, Cai X, Yang Z, Li H, Su X, Song M, Zhou D-S, Li X, Zhang C, et al. 2020. Identification of a functional human-unique 351-bp Alu insertion polymorphism associated with major depressive disorder in the 1p31.1 GWAS risk loci. Neuropsychopharmacology. 45(7):1196–1206.
Lo M-T, Hinds DA, Tung JY, Franz C, Fan C-C, Wang Y, Smeland OB, Schork A, Holland D, Kauppi K, et al. 2017. Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. Nat Genet. 49(1):152–156.
Lucassen PJ, Oomen CA, Naninck EFG, Fitzsimons CP, van Dam A-M, Czeh B, Korosi A. 2015. Regulation of adult neurogenesis and plasticity by (early) stress, glucocorticoids, and inflammation. Cold Spring Harb Perspect Biol. 7(9):a021303.
Luciano M, Hagenaars SP, Davies G, Hill WD, Clarke T-K, Shirali M, Harris SE, Marioni RE, Liewald DC, Fawns-Ritchie C, et al. 2018. Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism. Nat Genet. 50(1):6–11.
Luciano M, Huffman JE, Arias-Vásquez A, Vinkhuyzen AA, Middeldorp CM, Giegling I, Payton A, Davies G, Zgaga L, Janzing J, et al. 2012. Genome-wide association uncovers shared genetic effects among personality traits and mood states. Am J Med Genet. 159B(6):684–695.
Magnani R, Dirk LMA, Trievel RC, Houtz RL. 2010. Calmodulin methyltransferase is an evolutionarily conserved enzyme that trimethylates Lys-115 in calmodulin. Nat Commun. 1: 43.
Meier SM, Trontti K, Purves KL, Als TD, Grove J, Laine M, Pedersen MG, Bybjerg-Grauholm J, Baekved-Hansen M, Sokolowska E, et al. 2019. Genetic variants associated with anxiety and stress-related disorders: a genome-wide association study and mouse-model study. JAMA Psychiatry. 76(9):924–932.
de Moor MHM, van den Berg SM, Verweij KJH, Krueger RF, Luciano M, Arias Vasquez A, Matteson LK, Derringer J, Esko T, Amin N, et al. 2015. Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depressive disorder. JAMA Psychiatry. 72(7):642–650.
Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, Savage JE, Hammerschlag AR, Skene NG, Muñoz-Manchado AB, et al. 2018. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat Genet. 50(7):920–927.
Need AC, Goldstein DB. 2009. Next generation disparities in human genomics: concerns and remedies. Trends Genet. 25(11):489–494.
Ohi K, Otowa T, Shimada M, Sasaki T, Tanii H. 2020. Shared genetic etiology between anxiety disorders and psychiatric and related intermediate phenotypes. Psychol Med. 50(4):692–704.
Okbay A, Baselmans BML, De Neve J-E, Turley P, Nivard MG, Fontana MA, Meddens SFW, Linnér RK, Rietveld CA, Derringer J, et al. 2016. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet. 48(6):624–633.
Otowa T, Hek K, Lee M, Byrne EM, Mirza SS, Nivard MG, Bigdeli T, Aggen SH, Adkins D, Wolen A, et al. 2016. Meta-analysis of genome-wide association studies of anxiety disorders. Mol Psychiatry. 21(10):1391–1399.
Otowa T, Kawamura Y, Nishida N, Sugaya N, Koike A, Yoshida E, Inoue K, Yasuda S, Nishimura Y, Liu X, et al. 2012. Meta-analysis of genome-wide association studies for panic disorder in the Japanese population. Transl Psychiatry. 2(11):e186–e186.
Otowa T, Maher BS, Aggen SH, McClay JL, van den Oord EJ, Hettema JM. 2014. Genome-wide and gene-based association studies of anxiety disorders in European and African American samples. PLOS One. 9(11):e112559–e112559.
Otowa T, Yoshida E, Sugaya N, Yasuda S, Nishimura Y, Inoue K, Tochigi M, Umekage T, Miyagawa T, Nishida N, et al. 2009. Genome-wide association study of panic disorder in the Japanese population. J Hum Genet. 54(2):122–126.
Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 372:n71.
Peterson RE, Kuchenbaecker K, Walters RK, Chen C-Y, Popejoy AB, Periyasamy S, Lam M, Iyegbe C, Strawbridge RJ, Brick L, et al. 2019. Genome-wide association studies

in ancestrally diverse populations: opportunities, methods, pitfalls, and recommendations. Cell. 179(3):589–603.
Popejoy AB, Fullerton SM. 2016. Genomics is failing on diversity. Nature. 538(7624):161–164.
Purves KL, Coleman JRI, Meier SM, Rayner C, Davis KAS, Cheesman R, et al. 2019. A major role for common genetic variation in anxiety disorders. bioRxiv 203844. Available from: http://biorxiv.org/content/early/2019/04/11/203844.abstract.
Reuter MS, Tawamie H, Buchert R, Hosny Gebril O, Froukh T, Thiel C, Uebe S, Ekici AB, Krumbiegel M, Zweier C, et al. 2017. Diagnostic yield and novel candidate genes by exome sequencing in 152 consanguineous families with neurodevelopmental disorders. JAMA Psychiatry. 74(3):293–299.
Schizophrenia Working Group of the Psychiatric Genomics Consortium. 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 511:421–427.
Schosser A, Butler AW, Uher R, Ng MY, Cohen-Woods S, Craddock N, Owen MJ, Korszun A, Gill M, Rice J, et al. 2013. Genome-wide association study of co-occurring anxiety in major depression. World J. Biol. Psychiatry. 14(8):611–621.
Sheehan DV, Lecrubier Y, Harnett Sheehan K, Janavs J, Weiller E, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC, et al. 1997. The validity of the mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur. Psychiatry. 12(5):232–241.
Shifman S, Bhomra A, Smiley S, Wray NR, James MR, Martin NG, Hettema JM, An SS, Neale MC, van den Oord EJCG, et al. 2008. A whole genome association study of neuroticism using DNA pooling. Mol Psychiatry. 13(3):302–312.
Smith DJ, Escott-Price V, Davies G, Bailey MES, Colodro-Conde L, Ward J, Vedernikov A, Marioni R, Cullen B, Lyall D, et al. 2016. Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. Mol Psychiatry. 21(6):749–757.
Smoller JW, Block SR, Young MM. 2009. Genetics of anxiety disorders: the complex road from DSM to DNA. Depress Anxiety. 26(11):965–975.
Smoller JW. 2020. Anxiety genetics goes genomic. Am J Psychiatry. 177(3):190–194.
Sohani ZN, Sarma S, Alyass A, de Souza RJ, Robiou-du-Pont S, Li A, Mayhew A, Yazdi F, Reddon H, Lamri A, et al. 2016. Empirical evaluation of the Q-Genie tool: a protocol for assessment of effectiveness. BMJ Open. 6(6):e010403.
Spitzer RL, Kroenke K, Williams JBW, Löwe B. 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 166(10):1092–1097.
Stein MB, Chen C-Y, Jain S, Jensen KP, He F, Heeringa SG, Kessler RC, Maihofer A, Nock MK, Ripke S, et al. 2017. Genetic risk variants for social anxiety. Am J Med Genet B Neuropsychiatr Genet. 174(2):120–131.
Stevenson A, Akena D, Stroud RE, Atwoli L, Campbell MM, Chibnik LB, Kwobah E, Kariuki SM, Martin AR, de Menil V, et al. 2019. Neuropsychiatric genetics of African populations-psychosis (NeuroGAP-Psychosis): a case-control study protocol and GWAS in Ethiopia, Kenya, South Africa and Uganda. BMJ Open. 9(2):e025469.
Su X, Li W, Lv L, Li X, Yang J, Luo X-J, Liu J. 2021. Transcriptome-wide association study provides insights into the genetic component of gene expression in anxiety. Front Genet. 12:740134.
Tabarés-Seisdedos R, Rubenstein JLR. 2009. Chromosome 8p as a potential hub for developmental neuropsychiatric disorders: implications for schizophrenia, autism and cancer. Mol Psychiatry. 14(6):563–589.
Terracciano A, Sanna S, Uda M, Deiana B, Usala G, Busonero F, Maschio A, Scally M, Patriciu N, Chen W-M, et al. 2010. Genome-wide association scan for five major dimensions of personality. Mol Psychiatry. 15(6):647–656.
Van den Oord EJCG, Kuo P-H, Hartmann AM, Webb BT, Möller H-J, Hettema JM, Giegling I, Bukszár J, Rujescu D. 2008. Genomewide association analysis followed by a replication study implicates a novel candidate gene for neuroticism. Arch Gen Psychiatry. 65(9):1062–1071.
Walss-Bass C, Soto-Bernardini MC, Johnson-Pais T, Leach RJ, Ontiveros A, Nicolini H, Mendoza R, Jerez A, Dassori A, Chavarria-Siles I, et al. 2009. Methionine sulfoxide reductase: a novel schizophrenia candidate gene. Am J Med Genet B Neuropsychiatr Genet. 150B(2):219–225.
Waszczuk MA, Zavos HMS, Gregory AM, Eley TC. 2014. The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. JAMA Psychiatry. 71(8):905–916.
Weber H, Richter J, Straube B, Lueken U, Domschke K, Schartner C, Klauke B, Baumann C, Pané-Farré C, Jacob CP, et al. 2016. Allelic variation in CRHR1 predisposes to panic disorder: evidence for biased fear processing. Mol Psychiatry. 21(6):813–822.
World Health Organisation (WHO) 1992. International statistical classification of diseases and related health problems, tenth revision (ICD-10). World Health Organisation.
World Health Organisation (WHO) 1994. Schedules for clinical assessment in neuropsychiatry: version 2 (SCAN 2.1). World Health Organisation.
World Health Organisation (WHO) 2001. Composite international diagnostic interview, version 3.0. World Health Organization.
Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, et al. 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 50(5):668–681.