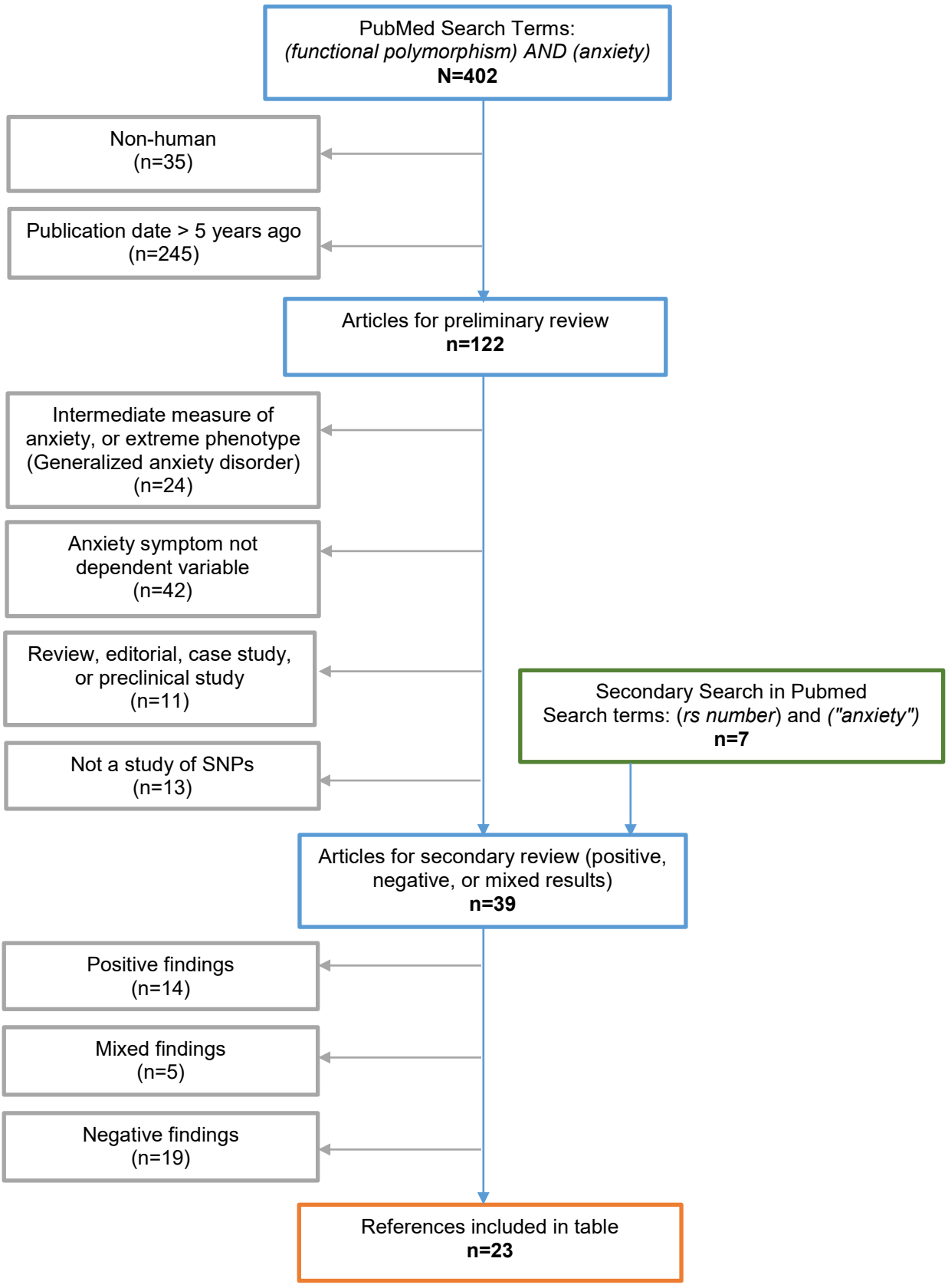
Supplemental Figure 1. Anxiety Search Results



Notes: Because of the vast amount of work done examining anxiety and the large number of studies returned from initial PubMed searches, “functional polymorphism” rather than “polymorphism” was used in the preliminary search. Of 402 English-language studies found using the search terms called out above, 35 non-human studies were removed and an additional 245 studies greater than 5 years old were removed. Given the focus of this synthesis, articles were excluded for a variety of reasons outlined above. While the studies identified used a variety of tools to measure severity of anxiety symptoms, “intermediate” measures of anxiety were ultimately removed. The following were considered intermediate measures of anxiety: social interaction anxiety, neuroticism, fear (i.e. startle response), emotional and sympathetic responses (i.e. skin conductance, cortisol levels), trait worry, harm avoidance, stress response, phobic anxiety. Additionally, it is important to note that studies in which the population examined included persons with generalized anxiety disorder (GAD) were excluded because this population was considered an extreme phenotype of anxiety. Furthermore, studies measuring “trait anxiety” were not included because this measure is considered “ingrained” and thus likely not modifiable.

Supplemental Table1. Evidence of Associations between Symptoms of Anxiety and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Anxiety Symptom Severity Tool	Context (i.e., sample details)	Relevant Findings
Quast et al., 2014, Germany	AKR1C1	rs3930965	Panic and Agoraphobia Scale (PAS)	Cohort 1: - n=522 participants with panic disorder; 69% female; mean age 37.1 ± 11.4 years Cohort 2: - n=290 participants with panic disorder; 71% female; mean age 36.1 ± 10.9 years Healthy controls: - n=573 healthy individuals; 74% female	Participants with the rs3930965 G/G genotype had significantly less anticipatory anxiety than those in the G/C and C/C groups (p=4.33x10^{-4} after correcting for multiple testing).
		rs41314625			Participants with the rs41314625 G/G genotype had significantly less anticipatory anxiety than those in the G/A and A/A groups (p=8.00x10^{-4} after correcting for multiple testing).
Konishi et al., 2014, Japan	BDNF	rs6265	State-Trait Anxiety Inventory (STAI)	- n= 470 participants with panic disorder; 62% female; mean age 37.9 ± 11.1 years - n=458 healthy controls; 57% female; mean age 36.6 ± 13.9 years	A gene × gene × gender interaction was observed in the association of the BDNF (rs6265) and COMT (rs4680) polymorphisms with STAI-state scores (p=0.018) in participants with panic disorder.
Marusak et al., 2016, USA	BDNF	rs6265	Screen for Child Anxiety Related Emotional Disorders (SCR-C)	- n=55 - Trauma group: 41.7% female; mean age 12.2 ± 2.3 years; 42.9% African American - Comparison goup:70.6% female; mean age 11.4 ± 2.6 years; 41.2% African American	Anxiety levels did not differ based on BDNF rs6265 genotype.
Svetel et al., 2013, Serbia	BDNF	rs6265	Hamilton Anxiety Rating Scale (HARS)	- n=177 Serbian patients with Parkinson's Disease; 33% female; mean age 58.9 ± 10.9 years - n=366 Controls (demographics not provided)	The BDNF rs6265 genotype did not influence anxiety in persons with Parkinson's Disease.
Pasparakis et al., 2015, Greece	CACNA1C	rs1006737	Visual Analogue Scale (VAS) anxiety	- n=194 healthy, right handed males - 100% Caucasian - established groups based on genotype (GG: 111; GA: 67; AA: 16)	At baseline, anxiety did not differ based on genotype groups (p>0.05). Following administration of instructions, the risk allele homozygotes (A/A) had a marked elevation of anxiety, evidenced by a genotype by occasion interaction [F(2.191)=15.3, p<0.001, n^2=0.136, power=0.99] and a genotype main effect [F(2.191)=7.3, p<0.001, n_p^2=0.070, power=0.93] confirmed with Bonferroni post hoc tests.
Sasaki et al., 2016, Japan	CHR	rs10474485	STAI	- Japanese sample - n=111 participants with irritable bowel syndrome; 58% female; mean age 21.9 ± 2 years - n=142 healthy controls; 46% female; mean age 22 ± 2.3 years - Japanese	Female A allele non-carriers showed significantly higher STAI-state (p=0.035). No difference was found in males.
Nees et al., 2013, Germany	CHRNA3	rs578776	Anxiety Sensitivity Index (ASI)	- Healthy adolescents from Germany, United Kingdom, Ireland, and France. Cohort 1: - n=487 non-smoking adolescents; 47% female; mean age 14.3 ± 0.3 years; 100% Caucasian Cohort 2 (replication cohort): - n=512 non-smoking individuals; 43% female; mean age 14.7 ± 0.3 years; 100% Caucasian	Cohort 1: Participants with the G/G genotype compared with A/G+A/A genotypes had significantly higher scores of anxiety sensitivity (p=0.037) Cohort 2: No significant association between genotype and anxiety sensitivity was found in the replication group (p>0.05)

				Note: samples partly overlap (n>300)	
Fernández-De-Las-Peñas et al., 2012, Spain	COMT	rs4680	Hospital Anxiety and Depression Scale (HADS)	- n=100 women diagnosed with fibromyalgia syndrome; mean age 52 ± 8 years	Post hoc comparisons with Holm-Bonferroni correction demonstrated women with fibromyalgia syndrome with the Met/Met genotype exhibited higher anxiety (F=13.385, p<0.001) than those with Val/Met and Val/Val genotype.
Mutschler et al., 2014, Switzerland	COMT	rs4680	STAI	- n=97 healthy females; mean age 23.6 years; 100% Caucasian - participant's anxiety was measured at baseline and again during MRI scanner delivered echoplanar imaging (EPI) stimuli presentation	At baseline (pre-MRI) Val/Val, Met/Met, and Val/Met carriers did not differ in terms of state-anxiety scores (F[2,94]=0.397, p=0.673, n_p^2=0.008). On average, Val/Val carriers, but not other participants, became more anxious during fMRI session. Participants with the Val/Val genotype had significantly higher state-anxiety compared to combined Val/Met and Met/Met group (F[1,95]=8.96, p=0.004, n_p^2=0.086).
Pardo-Lozano et al., 2012, Spain	COMT	rs4680	Evaluation of the Subjective Effects of Substances with Abuse Potential (VESSPA) Anxiety subscale	- n=27 healthy adults with recreational use of ecstasy (MDMA) on at least ten occasions (two in the previous year); 44% female; 100% Caucasian - EM phenotype for CYP2D6 activity determined using dextromethorphan as a selective drug probe - participants were given a single oral weight-adjusted dose of MDMA	Met/* allele carriers had significantly higher anxiety at 24 hours [$AUC_{0\text{-}24\ h}$ (p=0.025)] than Val/Val carriers.
Sheikh et al., 2013, Canada	COMT	rs4680	Preschool Age Psychiatric Assessment (PAPA) (anxiety score based on maternal interview)	<u>Cohort 1:</u> - n=413 pre-school aged children in Long Island, NY; 47% female; mean age 42.2 ± 3.1 months; 87.1% Caucasian	Preschool-aged children with the Val/Val genotype were found to have higher levels of anxiety as measured by the PAPA (p<0.05)
			Early Childhood Inventory-4 (ECI-4); parental interview	- n=362 pre-school aged children in Ontario, Canada; 51% female; mean age 43.2 ± 3.6 months; 90.5% Caucasian	No statistically significant relationship was found between genotype and level of anxiety as measured by ECI-4 (p>0.10)
Comasco et al., 2015, Sweden	FKBP5	rs3800373	Trauma Symptom Checklist for Children (TSCC)	- n=394 adolescents in "victimized" environment; 45.7% female; mean age 17.2 ± 0.7 years	Interaction effects between rs3800373 and environment were present (p=0.025). [See detailed results in referenced study in supplemental table 6b (Comasco et al., 2015)]
		rs1360780			Interaction effects between rs1360780 and environment were identified (p=0.023). [See detailed results in the referenced study in supplemental table 6b (Comasco et al., 2015)]
Udina et al., 2013, Spain	IL-6	rs1800795	HADS	- n=385 outpatients with Chronic Hepatitis C; 44% female; mean age 44.2 ± 10.2 years; 100% Caucasian - candidates to receive interferon alpha and ribavirin treatment	At baseline, there was no difference in anxiety based on genotype (p=0.13). During antiviral treatment, participants with the C/C genotype had significantly lower changes from baseline in IFN-induced anxiety (1.34; [0.43,2.25]; p=0.004). The mean scores differed significantly from baseline from week 24 onwards among G/C and G/G subjects (p=0.007) but did not change significantly over time among C/C subjects (p>0.2 at all-time points).
Beste et al., 2013, Germany	NSPR1	rs324981	ASI (German version) STAI	- n=97 healthy adults; 69% female; mean age 25.2 ± 6 years; 100% Caucasian	A statistically significant relationship between genotype and ASI score was identified. Participants with the A/A genotype had significantly lower ASI scores (F[2,94]=5.12; p=0.017; n_p^2=0.08). The A/T and T/T genotype groups did not significantly differ from each other (p>0.9). No significant relationship between NPSR1 genotype groups and STAI-state was found (r<0.1, p>0.5).

Guhn et al., 2015, Germany	NSPR1	rs324981	ASI STAI	- n=64 healthy volunteers; 50% female; mean age 25.4 ± 4.8 years; 100% Caucasian	No significant relationship between NPSR1 genotype and ASI (p=0.105) or STAI-state (p=0.9).
Laas et al., 2014, Estonia	NSPR1	rs324981	STAI	- Data originated in European Youth Heart study that consists of 2 birth cohorts (i.e., young & older) - study carried out in Estonian sample (n = 1176 [n=583 in younger cohort with mean age 9.6 years; n=593 in older cohort with mean age 15.6 years)	No significant relationship between NPSR1 and STAI-state anxiety alone was found However, when considering interaction models, there was a statistically significant difference between genotype groups. Positive interactions included, NSPR1 genotype and warmth (p=0.015), maltreatment (p=0.005), and stressful life events (p=0.023). Detailed results are presented in table 5 of the referenced article.(Laas et al., 2014)
Tupak et al., 2013, Germany	NSPR1	rs324981	ASI	- n=92 healthy, right handed, German adults; 66% female; mean age 24.4 ± 3.5 years	Anxiety did not differ between genotype groups (p=0.518).
Chang et al., 2017, Taiwan	SLC6A4	5-HTTLPR /rs25531	Beck Anxiety Inventory (BAI)	- n=1139 healthy Han Chinese individuals; 52% female; mean age 38.3 ± 10.3 years	S'S' homozygotic men had higher anxiety as measured by the BAI.
Hemmings et al., 2016, South Africa	SLC6A4	5-HTTLPR /rs25531	ASI	- n=951 South African adolescents (two ethnically diverse populations: n=634 Xhosa; n=317 Coloured)	The 5-HTTLPR-rs25531 L-G haplotype associated with reduced anxiety sensitivity among Xhosa adolescents (p= 0.010).
		rs1042173			The rs1042173 CC-genotype was protective against increased levels of anxiety sensitivity in Xhosa participants who had experienced increased levels of childhood trauma (p = 0.038). Additionally, Coloured males homozygous for the S-allele had increased anxiety sensitivity levels compared with Coloured males with at least one L-allele (p= 0.016).
Park et al., 2015, South Korea	SLC6A4	rs25531	Multidimensional Anxiety Scale for Children (MASC)	- n=64 offspring of persons with bipolar disorder; 53% female; mean age 13.7 ± 3.5 years; 9.4% non-Caucasians - n=51 healthy controls; 55% female; mean age 13.7 ± 2.7 years; 39.2% non-Caucasian	Offspring of persons with Bipolar disorder whom were naïve to antianxiety medication were found to have an association between 5-HTTLPR genotypes and anxiety symptoms; those with the s-allele showed higher level of overall anxiety than offspring of BD parents with the l/l genotype. No significant differences in anxiety symptoms or their association with the 5-HTTLPR genotype were found in the healthy control group.
Wilhelm et al., 2012, Australia	SLC6A4	rs25531	Patient Health Questionnaire (PHQ)	- n=234 patients with diabetes mellitus; 43% female; mean age 57.4 ± 13.5 years	The 5-HTTLPR/rs25531 genotype is associated with psychological distress in a sample of persons with diabetes.
Miaskowski et al., 2016, USA	TNFA	rs1799964	STAI	- n=398 women with breast cancer - Participants were divided into two distinct latent classes of anxiety trajectories (low versus high) - Lower anxiety class (n=147): mean age 57.5 ± 11.5 years; 77% White - Higher anxiety class (n=251): mean age 53.4 ± 11.3 years; 57.2% White	Controlling for age and rs3093662 genotype, carrying two of the rare C allele (T/T+T/C vs. C/C) was associated with an 88% reduction in the odds of belonging to the higher anxiety class. 0.12 (0.03-0.471) p=0.002
		rs3093662			Controlling for age and rs1799964, carrying 1 or 2 doses of the rare G allele (A/A vs. A/G+G/G) in TNFA rs3093662 was associated with a 4.04 increase in odds of belonging to the higher anxiety class. 4.04 (1.694-9.623), p=0.002 Overall model fit: x^2=42.81, p<0.0001
Kovacs-Nagy et al., 2013	WFS1	rs1046322	HADS	- n=801 healthy adults; 100% Caucasian (Hungarian)	Participants with the homozygous form of the rs1046322 minor allele (mm) reported significantly higher anxiety (F[1,797]=7.801, p=0.005, n_p^2=0.01, Power=0.797)

Abbreviations:
PAS: Panic and Agoraphobia Scale
STAI: State-trait Anxiety Inventory
SCR-C: Screen for Child Anxiety Related Emotional Disorders
HARS: Hamilton Anxiety Rating Scale
VAS: Visual Analogue Scale
ASI: Anxiety Sensitivity Index
HADS: Hospital Anxiety and Depression Scale
VESSPA: Evaluation of the Subjective Effects of Substances with Abuse Potential Anxiety subscale
PAPA: Preschool Age Psychiatric Assessment

ECI-4: Early Childhood Inventory-4
TSCC: Trauma Symptom Checklist for Children
BAI: Beck Anxiety Inventory
PHQ: Patient Health Questionnaire
MASC: Multidimensional Anxiety Scale for Children
USA: United States of America

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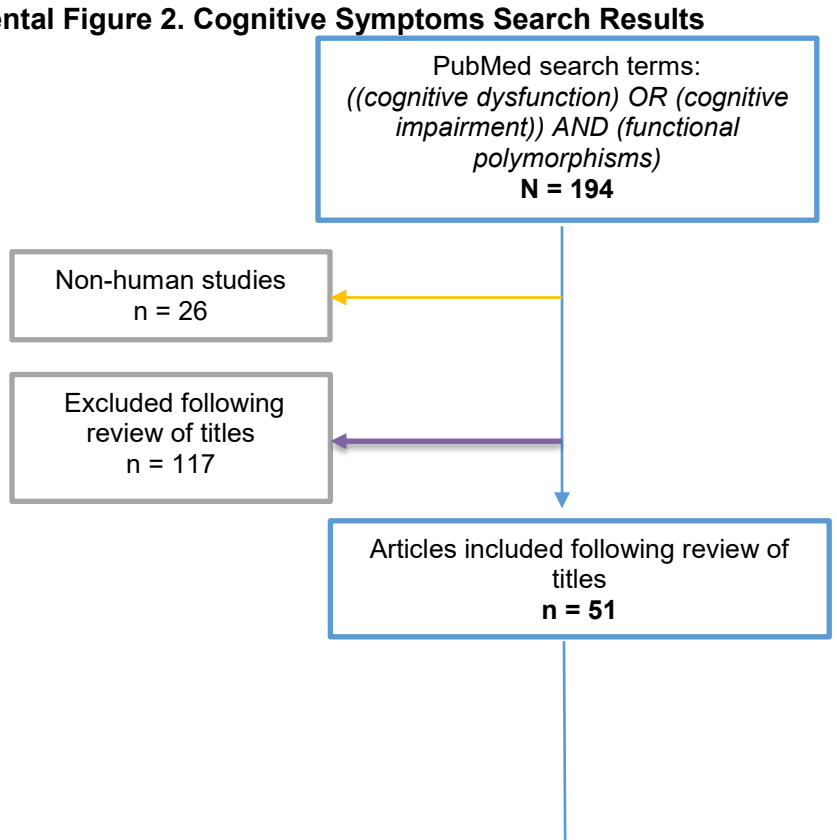
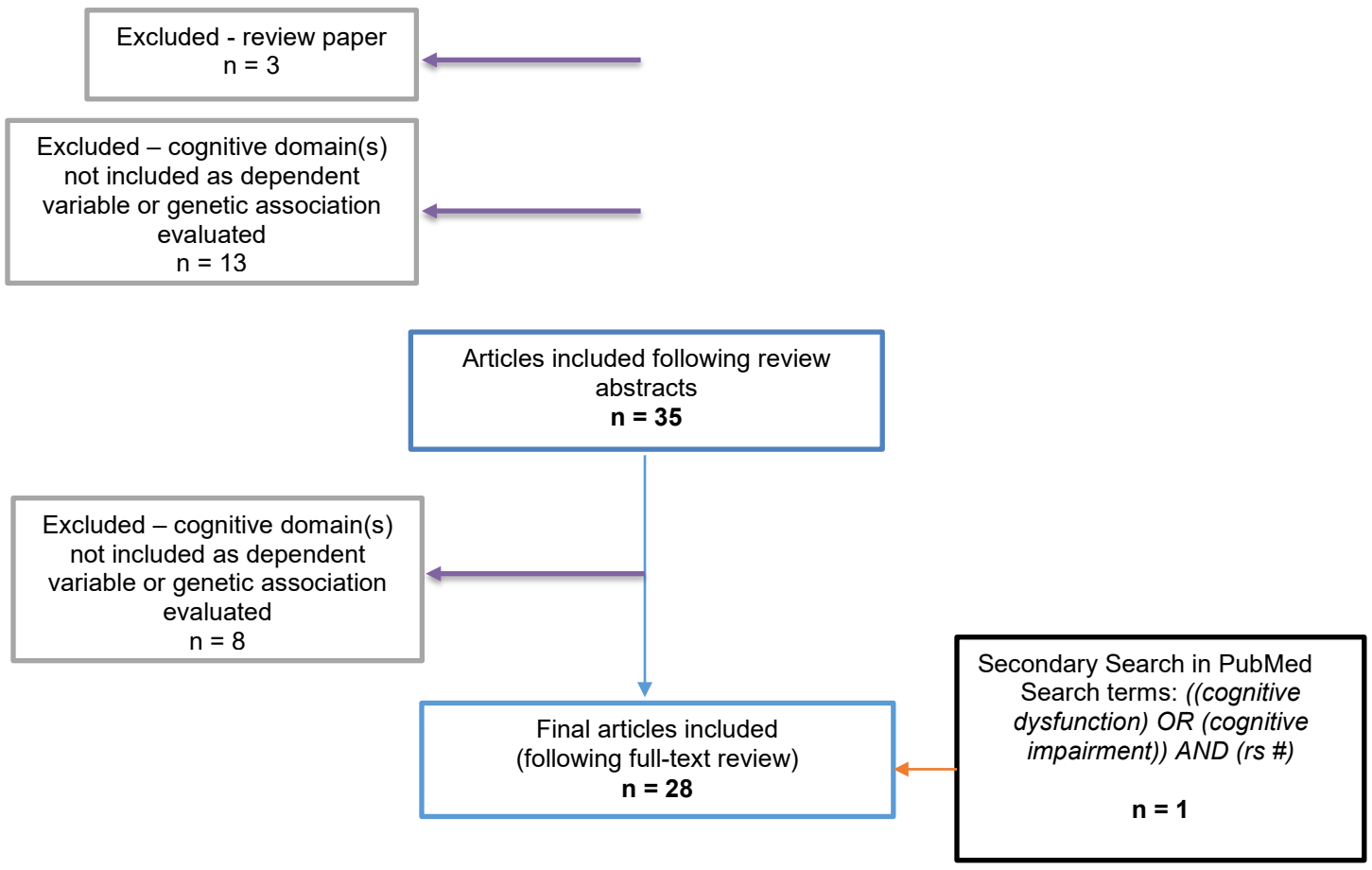
Supplemental Figure 2. Cognitive Symptoms Search Results





Notes: The initial search was conducted using the above mentioned key words. The following MESH terms were included in this search: ("cognitive dysfunction"[MeSH Terms] OR ("cognitive"[All Fields] AND "dysfunction"[All Fields]) OR "cognitive dysfunction"[All Fields] OR ("cognitive"[All Fields] AND "disturbance"[All Fields]) OR "cognitive disturbance"[All Fields]) AND (functional[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphisms"[All Fields]))

Supplementary Table 2. Evidence of Associations between Cognitive Symptoms and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Cognitive Symptom Phenotype(s)	Context (i.e., sample details)	Relevant Findings
Aas et al., 2012, Norway	*SLC6A4*	5-HTTLPR	Cognitive function: • Memory • Working memory & executive function • Perception & visuospatial abilities • Verbal abilities	Adult patients (*n* = 118) with psychotic disorders recruited from hospital-based psychiatric units in Oslo, Norway; 46% female. *n* = 50 subjects with schizophrenia spectrum disorders *n* = 53 subjects with psychotic affective disorders *n* = 15 with other psychoses	5-HTTLPR variations was associated with cognitive dysfunction; l-carriers performed better than s-carriers in memory tests (p = 0.008) Significant interaction effect: homozygotic s-carriers exposed to high levels of childhood trauma (physical neglect and abuse) had significantly poorer cognitive functioning than all other groups.
Azeredo et al., 2017, Brazil	*BDNF*	rs6265 (Val66Met)	Memory performance • Immediate verbal recall • Delayed verbal recall • Memory retention rate	*N* = 87 subjects who were > 55 years old were recruited using a community-based convenience sampling strategy in Porto Alegre, Brazil. Val/Val group: 78.7% female; mean age 68.6 ± 7.6 years Met allele carriers: 69.2% female; mean age 71.6 ± 8.5 years	Met allele carriers had lower delayed verbal recall scores (p = 0.004) and a decline in memory retention (p = 0.017) when compared to Val/Val homozygotes. No significant differences in immediate verbal recall between the two groups (p = 0.088).
Barratt et al., 2015, Australia	*MYD88*	rs6853	Cognitive dysfunction	N = 468 patients receiving transdermal fentanyl for cancer pain were recruited from the European Pharmacogenetic Opioid Study (EPOS); 53% female; mean age 64 ± 12 years.	Carriers of the MYD88 rs6853 variant were half as likely to have cognitive dysfunction (11/111 [10%]) than MYD88 rs6853 wild-type patients (21%) were twice as likely to have cognitive dysfunction than carriers of the variant (10%), with a relative risk of 0.45 (95% CI: 0.27 to 0.76) when accounting for major non-genetic predictors (age, Karnofsky functional score).
Bearden et al., 2004, USA	*COMT*	rs4680 (Val158Met)	Cognitive function: • General intellectual function • Memory • Language • Attention • Executive function • Visuomotor skills	N = 44 patients with confirmed 22q11.2 deletions (N = 44) were recruited through the Clinical Genetics Center at the Children's Hospital of Philadelphia; 61% female; mean age 11.1 ± 3.2 years; 95% Caucasian.	Met-hemizygous patients performed better than Val-hemizygous patients for executive function after controlling for IQ (F=5.03, df=1, 41, p<0.05). Met allele was associated with significantly better performance on the digit span task after controlling for IQ (F=4.38, df=1, 41, p<0.05) and superior performance on the Trails B test (F=3.57, df=1, 41, p=0.07).
Białecka et al., 2014, Poland	*BDNF*	rs6265	Cognitive impairment	n = 244 Parkinson disease (PD) patients were recruited in Outpatient Movement Disorder Clinics at two Polish centers; 51% female; mean age 64.2 ± 9.4 years. n = 242 randomly select healthy individuals were recruited from same geographical regions; 53% female; mean age 65 ± 9.4 years.	rs6265 was not associated with cognitive status in PD patients and healthy controls.. PD patients with Met/Met alleles had better delayed recall of information than those with Val/Val alleles after controlling for age, disease duration, and years of education (p=0.038).
Bosia et al., 2011, Italy	*HTR1A*	rs6295	Cognitive performance: • Intellectual functioning (Theory of Mind performance/abilities)	N = 118 clinically stable patients with schizophrenia were recruited from outpatient clinics; 36% female	Cognitive performance was predicted by rs6295 genotype (F = 5.03, df = 2, p = 0.008), IQ (F = 16.8, df = 1, p = 0.000) and executive function (i.e., planning) (F = 4.80, df = 1, p = 0.030).
Braida et al., 2015, Italy	*SNAP-25*	rs363050	Cognitive deficits	N = 44 Italian children with Autism Spectrum Disorder; 9% female; mean age 10.9 ± 4.7 years.	rs363050 associated with lower cognitive scores (p = 0.005). rs363050(GG) genotype was more frequent in subjects with lower cognitive scores than in subjects with higher cognitive scores (0.75 vs 0.25, p = 0.005).
Chae et al., 2016, Singapore*	*IL-6* *TNFA*	rs1800795 rs1800629	Cognitive function assessed using FACT-Cog and Headminder.	*N* = 125 Asian early-stage breast cancer patients (Stage I to III) receiving chemotherapy were prospectively recruited from two cancer centers in Singapore; mean age 50.3 years; 80.8% Chinese	No significant associations between polymorphisms and cognitive impairment.
Dickinson et al., 2014, USA	*SCN2A*	rs10174400	Cognitive ability: • General cognitive ability	GWAS discovery sample included 363 community	Schizophrenia group: rs10174400 genotype was associated with the 6

			• Verbal memory • Visual memory • N-back • Processing speed • Card sorting • Working memory span	control individuals (52.6% female; mean age 31.2 years) and 339 people with DSM-IV schizophrenia (22.7% female; mean age 34.9 years). Follow-up analyses studied 147 unaffected siblings of the schizophrenia cases and independent schizophrenia samples including a total of an additional 668 participants.	cognitive domains (i.e., general cognitive abilities, span, card sorting, processing speed, verbal and visual memory, N-back)(all *p*'s ≤ 0.02). Control group: Allelic trend for the control association with g was in the direction opposite the schizophrenia association, and an analysis of the interaction of rs10174400 genotype by group was also GWAS significance ($p = 1.75 \times 10^{-9}$). Follow-up analyses: In unaffected siblings, rs10174400 genotype was associated with and general cognitive abilities ($p = 0.03$). In 147 unaffected siblings, rs10174400 genotype was associated with years of education completed ($p = .003$), with T-allele carriers exhibiting reduced educational attainment compared to C-allele homozygotes.
Gajewski et al., 2013, Germany	*TNFA*	rs1800629 (-308 A/G)	Cognitive status: • Visual attention & vigilance (Digit-Symbol Test) *(Refer to manuscript for additional cognitive domains assessed, but had no significant genetic associations)*	N = 131 older healthy volunteers; 61.8% female; mean age 70.5 ± 4.5 years.	rs1800629 associated with digit-symbol test; total number of written symbols was higher in the GG than in the GA-AA subgroup (45.9 vs. 40.7; F(1,129) = 6.8; $p < 0.01$) and for the mean number of correctly written symbols (45.9 vs. 40.6; F(1,129) = 7.1; $p < 0.01$).
Gozal et al., 2012, USA	*NOX*	rs4673	Cognitive function deficits: • Differential Ability Scales (DAS) • NeuroPsychological Assessment Battery (NEPSY) Subjects were considered to have cognitive deficits if they scored 1 standard deviation below the mean for at least three subtests on either DAS or NEPSY batteries.	Children with Obstructive Sleep Apnea (OSA) were matched for age, gender, ethnicity, body mass index (BMI), the severity of sleep apnea, and maternal education. *N* = 69 children with OSA who exhibited altered neurocognitive Performances; 48% female; mean age 6.6 ± 0.5 years; 30% African American. *n* = 47 matched children with OSA who did not have any evidence of neurocognitive deficits; 49% female; mean age 6.7 ± 0.6 years; 30% African American.	rs4673 significantly different between 2 OSA subgroups (altered neurocognitive performances vs. those with no evidence of neurocognitive deficits) ($p < 0.01$). The frequency of rs4673 polymorphism was significantly less frequent among the children with cognitive deficits ($p < 0.02$).
Hoogland et al., 2010, Netherlands	*COMT*	rs4680 (Val158Met)	Cognitive performance: • Attention • Executive function	*N* = 153 early Parkinson Disease patients from outpatient clinics general hospitals in the Netherlands.	No association between *COMT* val158met genotype and cognitive performance.
Kobayashi et al., 2012, Japan	*NT-3*	rs6332	Cognitive function via the frontal assessment battery (FAB): • FAB total score • Similarities • Lexical fluency • Motor series • Conflicting instructions • Go/no-go • Prehension behavior	*N* = 215 Japanese outpatients with dementia (*n* = 168) and mild cognitive impairment (MCI) (*n* = 47) were recruited from memory outpatient clinics at Jikei University Hospital (Tokyo) or the Jikei University Kashiwa Hospital (Kashiwa City).	rs6332 genotype associated with conflicting instructions score among the 6 subtests ($p < 0.05$). In patients with mild AD, the conflicting instructions score differed significantly among the three genotypic groups of rs6332 ($p < 0.05$) (G/G < A/A: $p = 0.042$ and G/A < A/A: p = 0.041).
Levine et al., 2012, USA	*BDNF* *COMT* *DAT*	rs6265 (Val66Met) rs4680 (Val158Met) 3 VNTR	• Working memory • Processing speed • Learning • Memory • Motor	*N* = 184 HIV+ adults; 13.5% female; mean age 44.2 ± 8.5 years; 77.7% Caucasian.	No significant effects of polymorphisms or HIV disease severity on neurocognitive functioning.
Li et al., 2017, China	*SORL1*	rs1699102	Cognitive functions: • Mental status • Episodic memory • Attention & processing • Visual-spatial language ability • Executive function	*N* = 780 native Chinese, non-demented adults (> 50 years) in the Beijing Aging Brain Rejuvenation Initiative database; 63% female.	T allele associated with accelerated age-related change in episodic memory and processing speed tests (after controlling for group x age interaction; all *p's* < 0.03).
Ma et al., 2016, China	*APOE*	rs405509	Cognitive performances: • General mental status • Memory • Attention	*N* = 100 Chinese participants with fMRI imaging data who are in the Beijing Aging Brain Rejuvenation Initiative; age between 55 and 85 years; 59% female	Significant interaction between rs405509 and APOE status on general mental status, memory and attention ($p<0.05$).

Matsuzaka et al., 2017, Brazil	*COMT*	rs4680 rs165599 rs737865	Working memory: • Visual Working Memory (VWM) Task • Keep Track Task • Letter Memory Task	*n* = 212 individuals with schizophrenia; 31% female; 59% Caucasian *n* = 257 healthy controls (HCs) from 3 locations in Brazil; 61% female; 67% Caucasian	Significant association between rs4680 and rs737865 and Keep Track Task. (post-hoc Bonferroni p's = 0.042 and 0.043, respectively). rs165599 genotype*group interaction effect associated with VWM and Keep Track task performance in patients and controls, with AA carriers scoring lowest on both tests among controls, but highest among patients.
Myrum et al., 2015, Norway	*ARC*	*GWAS study, refer to manuscript for list of SNPs*	Cognitive function: • Semantic knowledge • Visuospatial ability • Estimated IQ • Episodic memory • Delayed episodic memory • Processing speed	*N* = 670 healthy subjects in the Norwegian Cognitive NeuroGenetics (NCNG) database	No significant associations with cognitive abilities.
Nagata et al., 2011a, Japan	*NGF*	rs6330	Cognitive function (executive function) via the frontal assessment battery (FAB): • FAB total score • Similarities • Lexical fluency • Motor series • Conflicting instructions • Go/no-go • Prehension behavior	*N* = 200 Japanese outpatients with dementia (*n* = 158) and mild cognitive impairment (*n* = 42) were recruited from memory outpatient clinics at Jikei University Hospital (Tokyo) or the Jikei University Kashiwa Hospital (Kashiwa City).	Significant differences identified for the go/no-go scores in between C/C and T carriers ($p < 0.01$). No significant differences in the other neuropsychological subtest scores reflecting attentional and memory function.
Nagata et al., 2011b, Japan	*BDNF*	rs2030324 (C270T) rs6265 (Val66Met [G196A])	Cognitive function (executive function) via the frontal assessment battery (FAB): • FAB total score • Similarities • Lexical fluency • Motor series • Conflicting instructions • Go/no-go • Prehension behavior	*N* = 169 elderly Japanese outpatients with dementia or amnestic mild cognitive impairment; 67% female.	FAB scores were significantly different between the rs2030324 genotypes (C/C and C/T) ($p = 0.003$). Subtest scores, conflicting instructions ($p = 0.001$) and prehension behavior ($p = 0.008$), significantly differed between rs2030324 genotypes. No significant associations between rs6265 genotypes and FAB scores.
Nagata et al., 2012, Japan	*BDNF*	rs6265 (Val66Met)	Cognitive function (executive function) via the frontal assessment battery (FAB): • FAB total score • Similarities • Lexical fluency • Motor series • Conflicting instructions • Go/no-go • Prehension behavior	*N* = 146 Japanese outpatients with dementia or amnestic mild cognitive impairment.	Patients with only a mild stage of AD: FAB total and go/no-go scores were significantly lower in those with Val/Val genotype than the Met carriers ($p < 0.05$).
Nedić et al., 2011, Croatia	*COMT*	rs4680 (Val158Met)	Cognitive function: • Cognitive status (Mini mental state examination [MMSE]) • Cognitive impairment (Alzheimer's disease assessment scale-Cog [ADAS-Cog]) • Visual attention (Visual association test [VAT]) • Verbal & visual memory (Word pairs learning and recall/picture pairs learning and recall [WPLCR/PPLR])	*n* = 46 patients with dementia (52% female) and *n* = 65 healthy older subjects (48% female). All patients were medication free, Caucasian, and of Croatian origin.	When compared to Met/Val or Val/Val genotypes, carriers of Met/Met genotype scored significantly lower on MMSE ($p = 0.043$), significantly longer time to respond to VAT duration of numbers test ($p = 0.030$), VAT time of response to numbers test ($p = 0.031$) and VAT average response to numbers test ($p = 0.031$), and significantly greater number of unanswered questions to WPLCR/PPLR ($p = 0.026$).
Ng et al., 2016, Singapore	*BDNF*	rs6265	Cognitive impairment assessed using Functional Assessment of Cancer Therapy-Cognitive Function	*N* = 145 patients receiving chemotherapy for early-stage breast cancer (mean age: 50.8±8.8 years; 82.1% Chinese)	Met/Met genotype was significantly associated with lower odds of developing cognitive impairment (odds ratio [OR] = 0.26; 95% CI: 0.08–0.92; $p = .036$). Met carriers were less likely to experience impairment in the domains of verbal fluency (OR = 0.34; 95% CI: 0.12–0.90; $p = .031$) and multitasking ability (OR = 0.37; 95% CI: 0.15–0.91; $p = .030$) compared with the Val/Val homozygote.
Oroszi et al., 2006, USA	*BDNF*	rs6265 (Val66Met)	Cognitive dysfunction (domains): • Memory • Attention/executive function • Visuospatial skills • Motor function • Psychomotor speed	*N* = 59 patients with systemic lupus erythematosus (SLE) with no previous or current central nervous system involvement; 78% female; mean age 41 ± 13 years; 53% Caucasian.	Met66 allele significantly associated with higher on psychomotor, attention/executive and motor function scores, and significantly higher domain Z scores for the psychomotor ($p = 0.005$) and motor ($p = 0.002$) domains.
Payton et al., 2005, United Kingdom	*SLC6A4*	16 or 17 bp VNTR2 HTTLPR	Cognitive decline: • Fluid intelligence (Heim intelligence tests parts one and two [AH and AH2]). • Vocabulary ability (Raven Mill Hill vocabulary scale part A [MHA]). • Processing speed (Random Letters [RL] test). • Memory (semantic memory [SEM], Immediate verbal Recall [IR], Delayed verbal	*N* = 758 elderly Caucasian volunteers (234 males and 524 females) involved in this study form part of the Dyne Steele DNA bank for cognitive genetic studies; 69% female; mean age 63 years.	Individuals homozygous for the VNTR2 12 alleles had a faster rate of cognitive decline for all cognitive tests compared to other genotypes; significance for both tests of fluid intelligence (AH1 $p = 0.002$, AH2 $p = 0.014$), the test of SEM ($p = 0.010$) and general cognitive ability ($p = 0.006$). No associations were observed between the HTTLPR polymorphism and cognitive decline, except homozygous individuals scored significantly higher on the delayed recall test ($p = 0.035$).

			Recall [DR] and Spatial Recall [SR]).		
Su et al., 2015, China	*BDNF*	rs6265 (Val66Met)	Cognitive functioning via Repeatable Battery for the Assessment of Neuropsychological Status [RBANS, Form A]: • Immediate memory • Visuospatial/constructional • Language • Attention • Delayed memory	*n* = 194 methamphetamine-dependent patients who were inpatients at Wenzhou Sanyang Detoxification Center; 18% female; mean age 31.5 ± 8.4 years. *n* = 378 healthy volunteers without history of drug use; 61% female; mean age 46 ± 13 years.	No significant associations between rs6265 genotypes and cognitive functioning (RBANS scores) after Bonferroni correction. In methamphetamine-dependent patients, BDNF x genotype interaction statistically significant on total score (p = 0.018), immediate memory index (p = 0.014), and visuospatial constructional index (p = 0.022).
Warburton et al., 2016, United Kingdom	*BDNF*	rs1491850	Cognitive dysfunction: • Memory • Psychomotor speed • Information processing	*N* = 82 adults newly diagnosed with epilepsy who had neuropsychological assessment and DNA sample and were part of the larger SANAD trials. 55% female; mean age 40 years; 100% Caucasian.	Significant association between genotype and memory function at both baseline (*NRSF*: rs1105434, rs2227902 and *BDNF*: rs1491850, rs2030324, rs11030094) and in thelongitudinal analysis (*NRSF*: rs2227902 and *BDNF*: rs12273363 [all p's < 0.05). Psychomotor speed was associated with genotype (*NRSF* rs3796529) in the longitudinal assessment.
		rs2030324			
		rs11030094			
		rs6265			
	NRSF	rs1105434			
		rs2227902			
		rs3796529			
Williams-Gray et al., 2008, United Kingdom	*COMT*	rs4680 (Val158Met)	Attentional control: • Task/behavioral performance	*N* = 29 medicated patients with early Parkinson disease; 38% female.	Patients with val/val genotype made fewer errors during intradimensional (ID) shifting problems than extradimensional (ED) problems; whereas those with met/met genotype performed equally for ID or ED shift.
Symptom Cluster Study					
Miaskowski et al., 2017	*CXCL8*	Haplotype: • rs4073 (A) • rs2227306 (C) • rs2227543 (C)	Mood-cognitive symptom cluster based on symptom severity (reported on MSAS) for: • Difficult concentrating • Feeling sad • Worrying • Itching • Feeling irritable	Patients (*n* = 157) with breast or prostate cancer at the completion of radiation therapy.	For each additional dose of the haplotype, the mood-cognitive symptom cluster score decreased by 39.0% (P = 0.009).
	NFKB2	rs1056890			Having two doses of the rare allele (i.e., CC+CT vs. TT) was associated with a 2.30-fold higher mood-cognitive symptom factor score (P = 0.014).
	IL-13	rs20541			As the dose of the rare allele increased (i.e., CC vs. CT vs. TT), the mood-cognitive symptom factor score decreased by 47% (P = 0.014).

* added from secondary search

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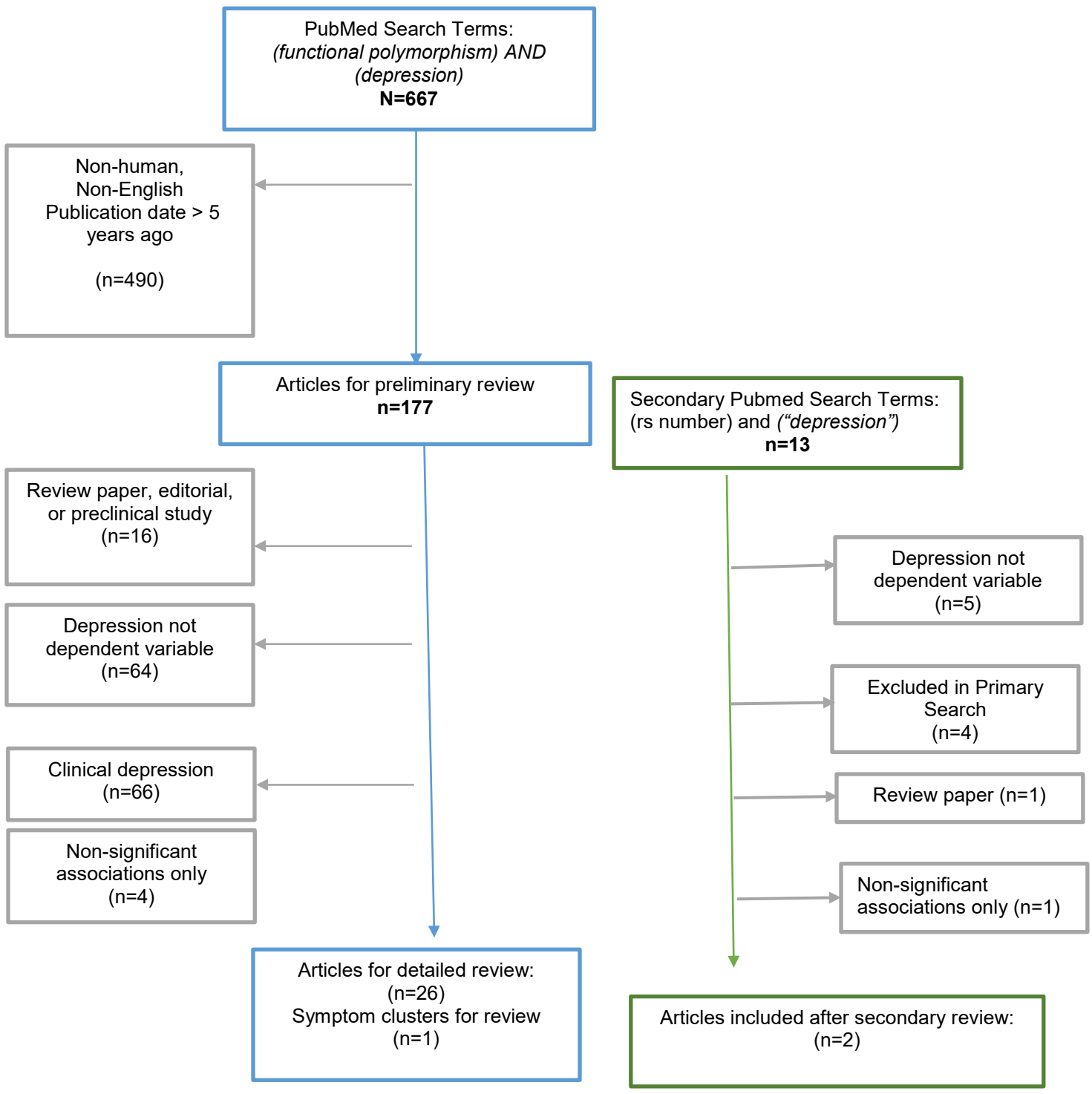
Supplemental Figure 3. Depressive Symptoms Search Results



Supplementary Table 3. Evidence of Associations between Symptoms of Depression and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Depression Symptom Phenotype(s)	Sample	Relevant Find
Avery et al., 2016, USA	HTR2C	rs6318	Diagnostic Inventory for Depression (DID) score	- n=112 non-depressed young adults from private Midwest university; 35% female	Significant main effect of g subclinical depressive sy (F(1,110) = 6.463, *p* = 0.0 exhibited significantly high (higher levels of subclinica symptoms) (M = 7.84, SD non-carriers (M = 5.58, SD
Brummett et al., 2014, USA	HTR2C	rs6318	Center for Epidemiologic Studies Depression Scale (CES-D) Mean score	- n=5078 young adults from large population-based sample in USA - 53% female; 100% Caucasian; mean age across genotype groups ~27 years	Significant interaction betw x life stress predicted CES women (*p* = .022) but not .471). Significant interaction of s genotype in a model with women (*p*=.025). In within-sex analyses, the genotype interaction pred among women remained (*p*=.011).
Bull et al., 2009, United Kingdom	IL6	rs1800795	Becks Depression Inventory (BDI) in UK and SDS in USA.	-n=98 -chronic HCV infection receiving IFN-α-2b and ribavirin. - recruited in London, UK and Atlanta, GA, USA - 46% female; 100% Caucasian	Subjects with CC genotyp fewer depressive symptom to GG/GC genotypes (F=9 *p*=.002). At week 24, there effect size difference betw and GG/GC groups. Subje CC genotype did not show significant increase in dep symptoms at any time poi compared with baseline (*p* 1.0); subjects with the GG showed a statistically sign in depressive symptoms a and 24 (*p*-value < 0.001–0
Comasco et al., 2015, Sweden	FKBP5	rs3800373	Trauma Symptom Checklist for Children (TSCC) - depression scale	- n=394 adolescents from Upper Secondary School Study in Sweden; 45.7% female; mean age 17.2 ± 0.7 years	When comparing 3 genoty CC) among 2 groups (adv events [ALE]>90th percen ALE<90th percentile) the Genotype on depression s significant *p*=0.001 as wel x Environment (*p*<0.001)
		rs1360780			When comparing 3 genoty TT) among 2 groups (ALE percentile, ALE<90th perc effect of the Genotype on score was significant *p*=0. Genotype x Environment

Eszlari et al., 2016, Hungary	MTHFD1L	rs11754661	Weighted Brief Symptom Inventory (BSI) depression score	- N=2204: Budapest, Hungary sample (n=895); Manchester, United Kingdom sample (n=1309) - 69.9% female; mean age 32.9 ± 0.2 years; 100% White	A allele associates positiv (significantly/trend) to BSI *p*=0.090 in an additive; β= *p*=0.058 in a dominant PL regression model). In Manchester sample, no association with BSI (β=0 in an additive; β=0.107, *p* dominant model) In Budapest sample, A all BSI depression score (β= in an additive; β=0.151, *p* dominant model)
Fasching et al., 2012, Germany	TPH2	rs10879354 rs11178993 rs6582071 rs11178997 rs7955501 rs17110536 rs4760814 rs7300641 rs4760820 rs1487275 rs10879358 rs11615016 rs17110747 rs1872824	Edinburgh Postnatal Depression Scale (EPDS)	- n= 361pregnant female; 100% Caucasian	A haplotype block in the p of TPH2 showed significa with depression values du pregnancy and 6-8 month pregnancy. SNPs not included in any haplotype blocks were an separately. Only rs10879 levels (T/T + T/C vs C/C), significant effect for time (and SNP ($p < 0.04$), but n interaction ($p < 0.79$). Pairwise comparison of th points showed a significan EPDS value at time 1 (pr time 2 (48-72 h postpartu 0.00001). When time 2 an months after birth) were c significant increase in EPI ($p < 0.001$).
Favaro et al., 2014, Italy	SCL6A4	5-HTTLPR short variant and AG SNP rs25531	Depression subscale of the Hopkins Symptom Checklist (HSCL)	- n=34 females with no history of psychiatric disorders; mean age 25.6 ± 6.6 years; 100% Caucasian	Significant interaction betw and the 5-HTTLPR genoty depression scores (F (3, 2 *p*=0.014; and F(3, 21)=3.2 using age as covariate (ge predicts different correlati between life stress and de symptoms).
Fernández-de-las-Peñas et al., 2012, Spain	COMT	rs4680	The hospital anxiety and depression scale (HADS)	- n=100 women with fibromyalgia; mean age 52 ± 9 years	Women with the Met/Met exhibited higher depressio than those with Val/Val an genotypes.
Gadow et al., 2014, USA	HTR2A	rs6311	Child Symptom Inventory (CSI-4) Severity of symptoms	- n=104 parents of children age 4-14 with ASD; 13% female; 90% White - Long Island, NY, USA	Significant main effect of g (F=5.20, *p*=0.025), with th having more severe depre than the A+ group, but the was small (ηp^2=0.049). When severity of generali disorder symptoms was c (F=7.87, *p*=0.006), the eff the moderate range (ηp^2=
Holz et al., 2015, Germany	FKBP5	rs1360780	Beck Depression Inventory (BDI) mean score	- n=153 young adults; 57% female	Significant genotype corre current BDI score and am

					connectivity emerged in th (r = .67, *p* = 0.01). Genotype-specific correla BDI reached trend level in (r =-.22, *p* = 0.07). Genotype-specific correla significant in the CC group 0.16). Significant correlation in T with the composite adulth scores.
Kim et al., 2012, South Korea	SLC6A4	5HTTLPR	Hamilton Depression Rating Scale (HAM-D)	- n = 186 Korean women with breast Cancer; mean age 54 years	The patients with the shor 5-HTTLPR had significant D scores (*p*=0.047).
Kovacs-Nagy et al., 2013, Hungary	WFS1	rs10002743 rs6824720 rs752854 rs4689393 rs10010131 rs13147655 rs4467645 rs13128674 rs6446482 rs4689395 rs28716718 rs1801208 rs734312 rs1046316 rs1046320 rs1046322 rs9457	Hospital Anxiety and Depression Scale-Depression Subscale (HADS) frequency	- n = 801 Caucasian, Hungarian participants; 53.8% female, mean age 21.3 - mean age 21.3 yrs - 46.2%, male - 100% of Caucasian - Hungary	Three WFS1 SNPs showe association with depressio rs1046322 (*p* =0.025), rs1 (*p*=0.009), rs6824720 (*p*= However, after Bonferroni SNP remained significant 0.0007).
Kovacs et al., 2016, Hungary	IL6	rs1800795	Brief Symptom Inventory (BSI) and Zung Self-rating Depression Scale (ZSDS)	-n=1053 European, White particiapnts; 70% female; mean age 31.2 ± 10.5 years	Interaction between rs180 recent negative life events assuming an additive or re heritability model, showed associations both with ZS depression scores. The in rs1800795 with pain back (PBGR) was significant as additive and dominant her case of BSI depression sc assuming all three heritab (additive, dominant, reces case of ZSDS score. After Bonferroni correctior affected significantly by th RLE interaction using a re For ZSDS scores, both ac recessive models of rs180 interaction remained signi rs1800795 x PBGR intera additive and dominant mo significant.
Kurrikoff et al. 2012, Estonia	NOS1	NOS1 ex1f-VNTR	Montgomery Asberg Depression Rating Scale (MADRS)	- n= 936 youth between ages 15-18 years; 27.9% female; 100% Caucasian	There is a significant three interaction effect between genotype,symptoms of de adverse life events (*p*=0.0 with one or two short allel adverse life events were r have more depressive sy similar relationship was fo

Lenze et al., 2008U USA	HTR1A HTR2A	HTR1A rs6295 (-1019C/G) HTR2A rs6311 (-1438A/G)	Geriatric Depression Scale (GDS)	n = 145 elderly women who had a hip fracture; mean age 81.2 ± 6.7 years; 4.1% African American	rs6295: those with a risk a significantly higher averag than those without the risk controlling for time since h age, comorbidities, and ac living (p = 0.009).
Lotrich et al., 2013, USA	BDNF SLC6A4	rs6265 5-HTTLPR	Montgomery-Asberg Depression Rating Scale (MADRS) severity; Beck Depression Inventory II (BDI-II)	- n= 124 euthymic patients during treatment with interferon-alpha therapy - Val/Met + Met/Met group: 35% female; mean age 50.8 ± 11.7 years; 87.8% Caucasian - Val/Val group: 26.5% female; mean age 47.1 ± 11.5 years; 87.4% Caucasian	rs6265 Met allele associat increased MADRS scores (p<0.001). Met allele only associated with an increas symptom on BDI-II – sadn and worthlessness (p=0.0 interaction between BDNF polymorphism and 5-HTTLPR (p=0.21).
Lovallo et al., 2014, USA	SCL6A4	5-HTTLPR. rs25531: low activity (SS, SLG, LGLG); Medium activity (SLA, LALG); and High activity (LALA)	Beck's Depression Inventory (BDI) score	- n=314 healthy young adults with and without a family history (FH) of alcoholism; 57% female; mean age 23.5 years; predominantly White	Significantly more sympto depression among the FH group, the High activity 5- subgroup (t = 3.31, p= 0.0 compared to their Low/Me counterparts. Multivariable indicated statistically signi HTTLPR interaction terms of depression (F = 6.80, p .022).
Ming et al., 2013, China	SLC6A4	5HTTLPR (rs25531)	Center for Epidemiologic studies Depression Scale (CES-D)	- n = 252 healthy, Chinese students; 52% female; mean age 16 ± 0.6 years	No significant association polymorphism and sympto depression.
Nilsson et al., 2014, Sweden	TFAP-2β	intron 1 Variable Number Tandem Repeat (VNTR)	Depression Self-Rating Scale (DSRS) severity	-Two independent cross-sectional samples from Sweden: Group A (n = 175; 62% female; all 19 year olds) and Group B (n = 1506; 48% female)	Group A: Significant main effect of genotype and sy ADHD on DSRS scores fo Group B: No effect of gen DSRS scores.
Porcelli et al., 2015, Italy	HTR1A	C-10119G of the (CC, CG, GG)	Hospital Anxiety and Depression Scale-Depression Subscale (HADS-D)	- n =130 patients with - chronic hepatitis C referred to tertiary care center for interferon (IFN) and ribavirin treatment; 53.3% female; mage age 51.1 ± 12.2 years - male,47.7%	Significant difference in H those with C/C, C/G, and 3 months (Mean 3.89, 5.4 p=0.002) and at End of Th Mean=3.47, 4.60, 8.75, p=

Rawson et al., 2015, USA	BDNF HTR1A SLC6A4	rs6265 rs6295 5HTTLPR-rs25531	Montgomery Asberg Depression Rating Scale (MADRS)	- n = 429 adults with hip fractures; 76% female; mean age 78.9 ± 8.5 years - n = 92 healthy comparisons; 65% female; mean age 78.3 ± 7.1 years; Combined sample: 93% White	BDNF Met/met carriers de significantly more depress than Val/Val carriers (*p*= 0 Epistatic effect between B 5HTTLPR-rs25531:2 LA a BDNF Met/Met genotype depressive symptoms afte (*p* = 0.006).
Saad et al., 2014, USA	INFGR1 TNFA IL6	rs9376268 rs1799964 rs2069840	Center for Epidemiologic studies Depression Scale (CES-D) used to determine symptom trajectory classes: Resilient (low CES-D that decreased slightly over 6 months) and Subsyndromal (CES-D that was just above clinically meaningful cut-point that increased slightly then decreased slightly over 6 months).	- Women who underwent breast cancer surgery on one breast with no metastasis - Resilient class: n = 155; mean age 57.3 ± 11 years; 69.5% White - Subsyndromal class: n = 180; mean age 53 ± 11.9 years; 62.6% White	rs9376268: Carrying A all GA/AA) was associated w increase in the odds of be subsyndromal class (OR = 0.022) while controlling fo score. rs1799964: Homozygous allele (TT/TC vs CC) asso 87% decrease in odds of subsyndromal class. (OR= while controlling for age a rs2069840: Homozygyous allele (CC/CG vs GG) ass 3.06x increase in odds of Subsyndromal class. (OR 0.023) while controlling fo score.
Sasaki et al., 2016, Japan	CRH CRH-BP	rs28364015 rs6472258 rs10474485	Self-rating Depression Scale (SDS)	- N = 253 adults with IBS or healthy - n = 111 IBS patients; 58% female; mean age 21.9 ± 2 years - n = 142 healthy controls; 46% female; mean age 22 ± 2.3 years	rs10474485 A allele asso lower SDS scores (*p* = 0.0 In the male subjects, there significant group (IBS/con rs10474485 genotype in t scores. In those with IBS-Mixed s (diarrhea & constipation), ignificantly higher SDS sc with the rs10474485 CC g those with AA or AC geno 0.03).
Van der Auwera et al., 2014, Germany	TPH2 SLC6A4	rs7305115 5-HTTLPR (Short and Long variants) - rs25531	Beck Depression Inventory II (BDI-II) for LEGEND study. Patient Health Questionnaire (PHQ-9) for TREND scores.	Two independent samples (LEGEND & TREND) of Caucasian adults from the study of health in Pomerania, Germany: - LEGEND sample: n = 2029; 52% female - TREND sample n = 2475; 51% female.	Significant interaction effe TPH2 rs7305115 x 5-HTT genotype) on depression 0.023): 5-HTTLPR SS ge associated with increased scores after childhood abu carriers of low expression genotype, whereas there opposite relationship with genotype. .
Vinkers et al., 2015, Netherlands	MR gene NR3C2	MR haplotypes (GA, CA, & CG; rs2070951 and rs5522)	Population-based cohort: Beck's Depression Index (BDI) score Clinical cohort: Inventory of Depressive	Two sample cohorts: - n = 665 population-based cohort of young adults and adolescents; 56% female; mean age 21 years. - n = 1639 participants from Netherlands Study of Depression	CA haplotype moderated between child maltreatme depressive symptoms in b < 0.03). Relationships we dependent: females in the based cohort were protec whereas males in the clini were at increased risk (*p* = Decreased lifetime risk fo

			Symptomatology (IDS-SR30) score	and Anxiety (current or past anxiety or depression disorder and healthy controls); 66% female; mean age 42 years.	was identified in male GA increased risk for male CA clinical sample.
Xu et al., 2013, China	SLC6A4	5HTTLPR (rs25531)	Hamilton Depression Rating Scale (HDRS) severity	- n = 96 SLE patients; - n = 96 healthy controls matched by age & sex Combined demographics: 76% female, 100% Han Chinese.	There was a higher freque allele (L) in non-depressiv depressive SLE (p =0.006 homozygotes reported sig higher mean HDRS score with SL/LL genotypes.
Zhang et al., 2016, China	BDNF	rs6265	Children's Depression Inventory (CDI) score	- n = 780 Han Chinese adolescents drawn from Beijing Twin Study (only 2nd born child was genotyped); 51% female; mean age 13.6 years.	rs6265 significantly mode relationship between relat between maternal warmth depressive symptoms. Va less depressive symptoms homozygotes.
Zhou et al., 2013, China	BDNF	rs6265	Center for Epidemiologic studies Depression Scale (CES-D) Chinese version severity	- n = 296 type 2 diabetes (T2DM) patients; this group was divided into 2 subgroups – depressive (DDM) and non-depressive (NDDM) - n = 70 healthy volunteers - Han Chinese - Mean age of NDDM group 53.1, Mean age of DDM group 54.3 - NDDM group: 44.4% of female, DDM group: 70.3% of female - The diabetes group was divided into 2 subgroups	The DDM group were mo carriers of the Met allele (the NDDM (38.8%) and h (39.3%) (p<0.05).

Abbreviations:
BDI = Beck Depression Inventory
BDI-I = Beck Depression Inventory I
BDI-II = Beck Depression Inventory II
BSI = Brief Symptom Inventory
CDI = Children's Depression Inventory
CES-D = Center for Epidemiologic studies Depression Scale
CSI-4 = Child Symptom Inventory
DDM = depressive diabetes group
DID = Diagnostic Inventory for Depression
DSRS = Depression Self-Rating Scale
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV
EPDS = Edinburgh Postnatal Depression Scale
FMS = Fibromyalgia Syndrome

GDS = Geriatric Depression Scale
HADS = Hospital Anxiety and Depression Scale-Depression Subscale
HAM-D = Hamilton Depression Rating Scale
HDRS = Hamilton Depression Rating Scale
HSCL = Depression subscale of the Hopkins Symptom Checklist
IDSR-30 = Inventory of Depressive Symptomology
KPS = Karnofsky Performance Scale
MADRS = Montgomery Asberg Depression Rating Scale
NDDM = non- depressive diabetes group
PHQ-9 = Patient health questionnaire
SDS = Self-rating Depression Scale
SDQ = Strengths and difficulties questionnaire- depression subscale
SDS = Zung Self-Rating Depression Scale
SLE = systemic lupus erythematosus
ZSDS = Zung Self-Rating Depression Scale

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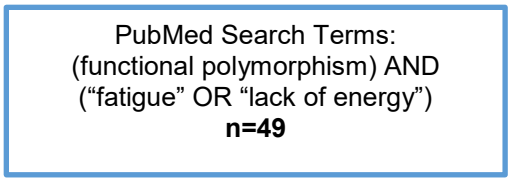
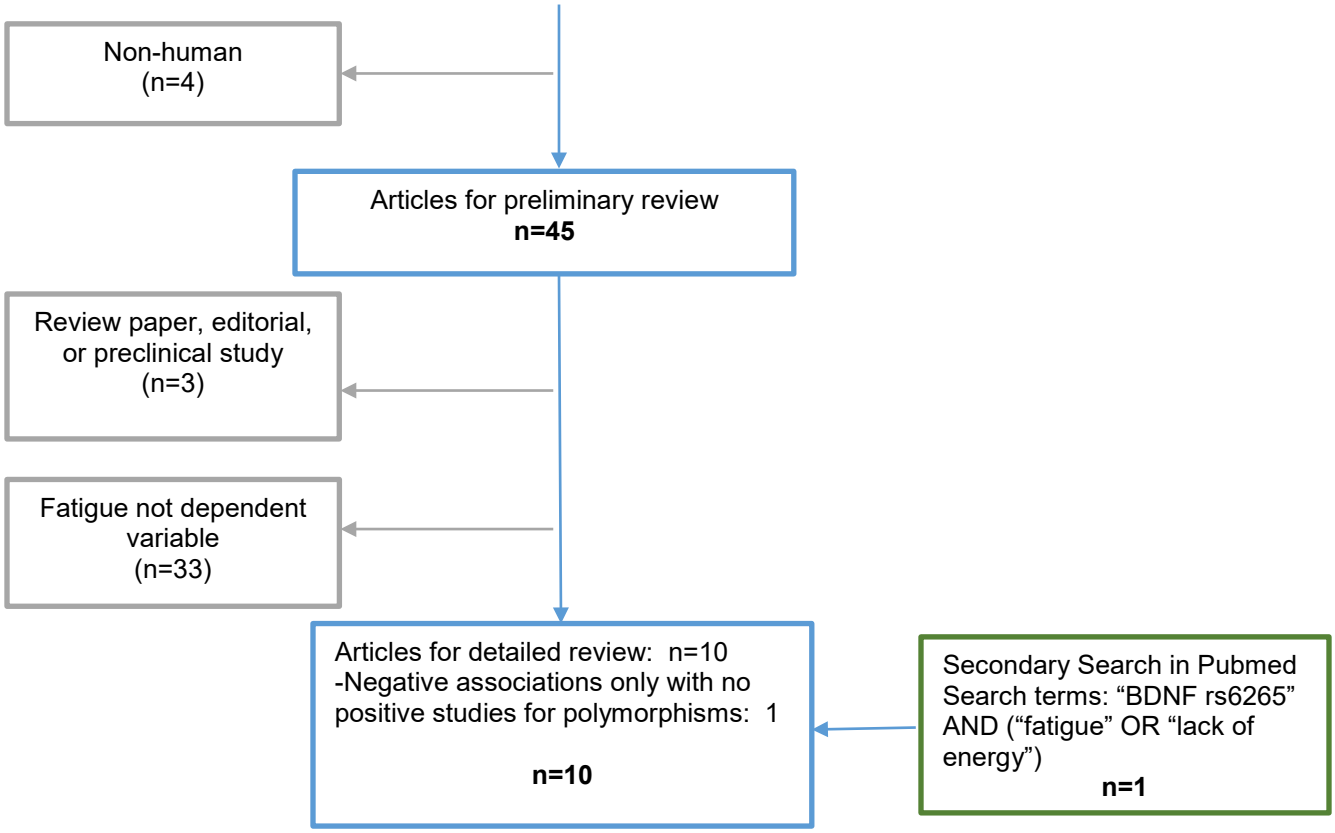
Supplemental Figure 4. Fatigue Search Results





Notes: Articles with chronic fatigue syndrome as the outcome (phenotype) were excluded from this search.

Supplementary Table 4. Evidence of Associations Between Fatigue and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Fatigue Symptom Phenotype(s)	Context (i.e., sample details)	Relevant Findi
Aouizerat et al., 2015, USA	*IL2*	rs1479923	severity	- n = 252 patients who had primary or adjuvant radiation therapy and their family caregivers - Mean age 61.5 years; most participants were female, Caucasian, well educated, and married/partnered.	Being homozygous for the rare T associated with a 75% decrease i belonging to the low morning ene
	NFKB1	rs4648110			Being heterozygous or homozygo allele was associated with a 42% odds of belonging to the low morn (*p*=.046).
	IL1R2	rs4141134			Heterozygous or homozygous for was associated with a 64% decre belonging to the moderate evenin (*p*=.019).
	IL6	rs4719714			Being heterozygous or homozygo allele was associated with a 73% odds of belonging to the moderat class (*p*=.001).
	IL17A	rs8193036			Being heterozygous or homozygo allele was associated with a 61% odds of belonging to the moderat class (*p*=.011).
	NFKB2	rs1056890			Being homozygous for the rare T associated with a 9.7-fold increas belonging to the moderate evenin (*p*=.032).
	TNFA	rs1800683			Being homozygous for the rare A associated with a 64% decrease i belonging to the moderate evenin (*p*=.022)
Aouizerat et al., 2009, USA	TNFA	rs1800629	severity	- n = 253 cancer outpatients (168 patients with breast, prostate, lung, or brain cancer and 85 of their family caregivers) - 53.8% female; mean age 61.4 ± 11.3 years; 74.6% White	Controlling for age, common allel a mean morning fatigue score tha points higher than minor allele ca
Bull et al., 2009, United Kingdom	IL-6	rs1800795	severity	- n = 98 - Caucasian, - chronic HCV infection with compensated liver disease	IL-6 rs1800795 was not associate fatigue (*p*=.2); 5-HTT: *p*=.5).
	5-HTT	5-HTTLPR			5-HTT 5-HTTLPR was not associ of fatigue (*p*=.5).
Eshragh et al., 2017, USA	ADRB2	rs1042718	severity	- n = 397 women who underwent unilateral breast	Carry one or two doses of the rar associated with an 87% lower odd the higher fatigue class (*p*=.008).

	BDNF	rs6265		cancer surgery	Carry one or two doses of the rare associated with a 50% lower odds higher fatigue class (*p*=.020).
	COMT	rs9332377			Carry one or two doses of the rare associated with a 52% lower odds higher fatigue class (*p*=.026).
	CYP3A4	rs4646437			Carry one or two doses of the rare associated with a 52% lower odds higher fatigue class (*p*=.025).
	GALR1	rs949060			Carry two doses of the rare C alle with a 2.46-fold higher odds of be fatigue class (*p*=.020).
	GCH1	rs3783642			Carry one or two doses of the rare associated with a 53% lower odds higher fatigue class (*p*=.014).
	NOS1	rs9658498			Carry two doses of the rare C alle with a 55% lower odds of belongi fatigue class (*p*=.029).
	NOS1	rs2293052			Carry two doses of the rare T alle with a 4.58-fold higher odds of be fatigue class (*p*=.004).
	NPY1R	Haplotype A04			Each additional does of NPY1R H associated with a 1.77-fold higher to the higher fatigue class (*p*=.003
	SLC6A2	rs17841327			Carry two doses of the rare A alle with a 10.31-fold higher odds of b higher fatigue class (p=.003).
	SLC6A4	5HTTLPR + rs25531			Carry one or two doses of the L_A a with a 47% lower odds of belongi fatigue class (p=.023).
Malyuchenko et al., 2010, Russia	DAT1	VNTR	severity	- n = 140 student volunteers - 50% female; mean age 20 ± 1 years	A significant relationship between and *COMT* gene polymorphism a mental sphere status were reveal these polymorphisms were the m girls.
	DRD2	Taq I			
	COMT	Val66Met			
Miaskowski et al., 2010, USA	IL-6	rs4719714	severity	- n = 253 (168 patients with breast, prostate, lung, or brain cancer and 85 of their family caregivers). - 53.8% female; mean age 61.4 ± 11.3 years; 74.6% White	Common allele homozygotes repo evening fatigue (*p* = .003), mornin and sleep disturbance (*p*=.003) th carriers.
Piraino et al., 2012, Australia	IFN-γ	rs2430561	severity	- n = 296 Caucasian, adult participants in the Dubbo Infection Outcomes Study	The T allele of the IFN-γ +874 T/A associated with increased *fatigue* addition, females were more likely fatigue extreme (*p* = 0.01) while in

				- 49% women; mean age 34.2 years	infection were less likely to suffer (p = .02).
Udina et al., 2013, Spain	IL-6	rs1800795	intensity	- n = 385 Caucasian outpatients with chronic hepatitis C who were starting IFN-alpha and ribavirin treatments - 44% female; mean age 44.2 ± 10.2 years	Baseline values of the VAS scale differences between GG & GC an (p = 0.046)
Illi et al., 2012, USA	IL-4	rs2243248	severity	- n = 253 cancer outpatients (168 patients with breast, prostate, lung, or brain cancer and 85 of their family caregivers) - 53.8% female; mean age 61.4 ± 11.3 years; 74.6% White	Carrying the minor allele for IL4 rs was associated with over a sixfold odds of belonging to the "All high" along with younger age, being Wh (vs a FC), having a lower function a higher number of comorbid con
Doong et al., 2015, USA	IL-6	rs2069845		- n = 398 women who underwent unilateral breast cancer surgery	rs2069845 significantly associated membership (p = .013).
	IL-13	rs1295686			rs1295686 significantly associated latent class membership (p =.013
	TNF- α	rs1800610			rs1800610 significantly associated membership (p = .040).

Abbreviations:
FC: Family caregiver
RRV: Ross River Virus
VAS: Visual analogic scale

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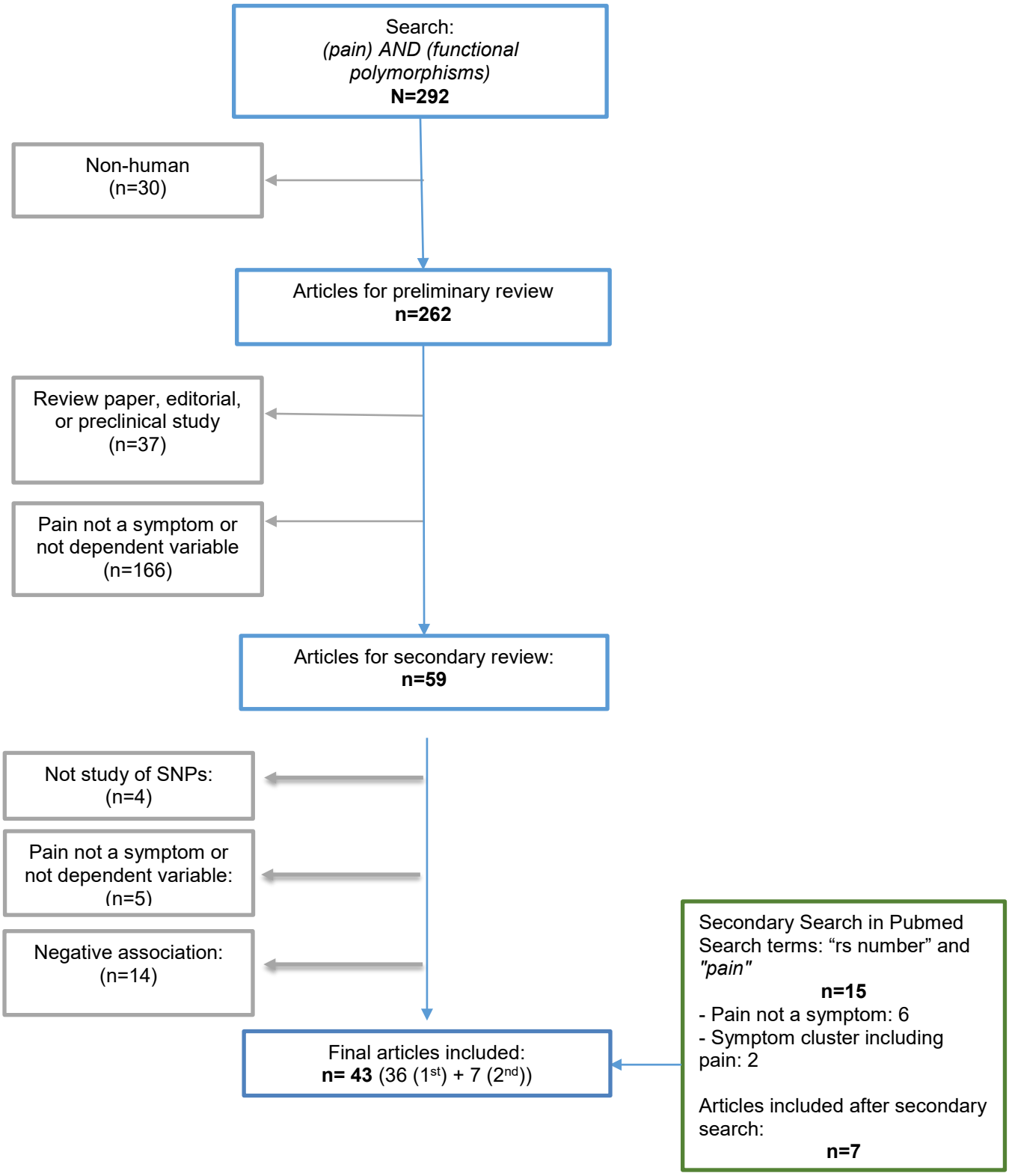
Supplemental Figure 5. Pain Search Results



Notes: Of 292 English-language studies found using the search terms, 183 were >5 years old; however, all studies regardless of publication date were included. Pain was defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such

damage" by the International Association for the Study of Pain (IASP) at https://www.iasp-pain.org/Taxonomy#Pain.

Supplemental Table 5. Evidence of Associations between Symptoms of Pain and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Pain Symptom Phenotype(s)	Sample	Relevant Findings
Applebaum et al., 2015, USA	COX-2	**Haplotype** rs2383515 rs5277 rs5275 rs2206593	Severity	- n=94 patients treated with non-surgical root canal therapy; 43% female; mean age 48 ± 2.2 years; 70% Caucasian	COX-2 haplotype significantly associated with day 1 worst pain rating following endodontic treatment (p=0.025)
Ballina et al., 2013, USA	OPRM1	rs1799971	Pain severity Mean # of regions of moderate or severe pain (defined by a pain score ≥ 4 on a 0-10 NRS)	- n=52 European American women sexual assault (SA) survivors	Women with ≥1 G alleles at A118G: - had decreased pain severity during the initial 6 weeks after SA (p = .002). Significance maintained after adjusting for age, income, education, prior overall pain, and overall pain (p=0.0004). - had significantly lower overall pain scores 1 week after SA (p=0.002) and 6 weeks after sexual assault (p= .018). - Significantly fewer body regions with moderate or severe pain during initial 6 weeks (p=0.002). - Significantly lower number of body regions with moderate or severe pain 1 week after SA (p=0.002) and 6 weeks after SA (p=0.014). - No significant association prior to SA
Belfer et al., 2013, USA	COMT	rs165599	Pain sensation Burn sensation Severity	<u>Cohort 1</u>: - n=35 healthy subjects; 87.5% female;18-45 years old; 75.1% Caucasian <u>Cohort 2</u>: - n=108 healthy adults; 51.9% female; mean age	rs165599 was associated with the thermal pain ratings to the initial first pulse from the train of 10 pulses delivered at 47℃ (p=0.02) or 50℃ (p=0.04).
		haplotype rs6269 rs4633 rs4848			- HPS haplotype showed the greatest difference and sensitivity to capsaicin. Effect was significant for females (p = 0.04 & p=0.02,

		rs4680 **HPS**: ACCG **LPS**: GCGG		28.6 ± 8.6 years; 50.9% Caucasian	respectively), but not for males (*p*=0.43 and 0.54, respectively). - HPS/LPS haplotype had significantly higher pain ratings than participants with the LPS/LPS haplotype at both 47℃ (*p*=0.002) and 50℃ (*p*=0.0006).
Bondy et al., 1999, Germany	5-HT2A	rs6313	Severity	- n=168 fibromyalgia patients; 85% female; mean age 53.9 ± 10.6 years; 100% Caucasian	People with T/T genotype had significantly higher self-reported pain scores (*p*=0.028)
Bortsov et al., 2013	FKBP5	rs3800373	Severity	Discovery Cohort : - n=949 European Americans who had a motor vehicle collision; 61% female; mean age 36 ± 13 years Replication Cohort: - n=53 European American women experiencing sexual assault; mean age 27 ± 8 years	For the discovery cohort: - the presence of one or more minor alleles 8 SNPs [rs380073 (*p*<0.001), rs7753746 (*p*<0.001), rs3777747 (*p*=0.002), rs4713902 (*p*=0.002), rs9380526 (*p*<0.001, rs9394314 (*p*=0.001), rs2817032 (*p*=0.002), rs2817040 (*p*=0.008)) predicted neck pain severity six weeks after MVC. Six of these SNPs [rs380073 (*p*=0.003), rs7753746 (p=.001), rs9380526 (*p*<0.001), rs9394314 (*p*=0.003), rs2817032 (*p*=0.006), rs2817040 (*p*=0.004)] also predicted overall pain. For the replication cohort: - the presence of one or more minor alleles 3 SNPs [rs380073 (*p*=0.035), rs9380526 (p<.001, rs9394314 (*p*=0.042), rs2817032 (*p*=0.019)) predicted neck pain severity six weeks after sexual assault. 4 SNPs [rs380073 (*p*=0.029), rs9394314 (*p*=0.011), rs2817032 (*p*<0.001), rs2817040 (*p*=0.013)] also predicted overall pain.

Camilleri et al., 2009, USA	mtDNA	3010	Occurrence (abdominal pain)	- n=699 patients with/without FGIDs, diarrhea-predominant IBS, or functional diarrhea; predominantly Caucasian	Among those with 7028C, nonspecific abdominal pain (chronic abdominal pain or dyspepsia) was significantly associated with 3010A compared with 3010G (OR=3.3, *p*=0.02),
Cheng et al., 2010, Taiwan	OPRM1	rs1799971	Occurrence (foot ulcer pain)	- n=65 Taiwanese diabetic foot ulcer patients (DFU) - 2 pain groups: painful DFU (n=15; 26.7% female; mean age 67.5 ± 16.8 years) and painless DFU (n=50; 48% female; mean age 65 ± 11.8 years)	- Significant difference between genotype frequency between painful DFU and painless DFU groups (OR=0.24; *p*= 0.38) - The distributions of Taiwanese A118G genotypes are significantly different from those of Caucasians (*p*=0.003), pregnant Hispanic women (*p*=0.005), African Americans (*p*<0.001), and European Americans (*p*<0.001).
Dogru et al., 2016, Turkey	TNF	rs1800629	Occurrence	- n1=154 female patients with dysmenorrhea; mean age 25.5 ± 4 years - n2=144 healthy female controls; mean age 26 ± 4.3 years	The genotype and allele frequencies of -308G > A polymorphism showed statistically significant differences between dysmenorrhea patients and controls (p = 0.023 and p = 0.009, respectively). Significant association when the patients were compared with the controls according to the GG genotype versus GA+AA genotypes (p = 0.009)
Eroglu et al., 2016, Turkey	GSTP1	rs1695	Severity	- n1=140 women diagnosed with carpal tunnel syndrome (CTS); mean age 46 ± 11.8 years - n2=97 healthy controls; mean age 30 ± 4.4 years -All participants were non-working women	Genotypes were associated with pain severity ratings ($p \leq 0.015$). Subgroup analysis showed CTS patients with the Ile/Val genotype had significantly higher scores on the VAS and Boston SSS than those with the Ile/Ile genotype of GST P1 Ile105Val polymorphism (*p*=0.006 and 0.017, respectively). Patients with the Ile/Val or Val/Val genotypes had significantly higher VAS and Boston SSS scores compared to those of the patients with

					the Ile/Ile genotype (p=0.003 and 0.004, respectively).
Furquim et al., 2016, Brazil	TNFA	rs1800629	Occurrence Sensitivity	- n1=152 patients with Temporomandibular joint disorder (TMD); 89% female; mean age 36.1 ± 11 years - n2=91 sex- and age-matched healthy controls; 90% female; mean age 34.7 ± 11.5 years	rs1800629 positively associated with TMD. Subjects with TMD had a 2.87 times greater chance of having the GA genotype than did the control group. Homozygotes of minor allele (A) had decreased pain sensitivity for the temporomandibular joint and anterior fascicle of the temporal muscle in the pressure pain threshold test compared with wildtype.
Heimann et al., 2013, Germany	SCN9A	**Haplotype** rs41268673 rs6746030	Pain threshold	- n=95 healthy Caucasian participants	Pain threshold increased with increasing number of wild-type SCN9A haplotype alleles rs41268673C/rs6746030C. The wild-type haplotype rs41268673C/rs6746030C) also modulated the pressure pain threshold (Jonckheeres trend test p=0.033 one-sided). Pressure pain thresholds were significantly modulated by the rs41268673A/rs6746030C haplotype (p=0.022)
Henstrom et al., 2014, Sweden	NPSR1	rs714588	Occurrence (recurrent abdominal pain)	- n=1774 12-year-old children from the Swedish birth cohort BAMSE	Significantly associated with recurrent abdominal pain (OR: 1.44, p = 0.033)
		rs2530552			Significantly associated with recurrent abdominal pain (OR: 1.47, p = 0.022)
		rs2530566			Significantly associated with recurrent abdominal pain (OR: 1.55, p = 0.014)
		rs963218			Significantly associated with recurrent abdominal pain (OR: 1.49, p= 0.022)
		rs2531840			Significantly associated with recurrent abdominal pain (OR: 1.41, p = 0.034)

Herlyn et al., 2010, Germany	ADRA1A	rs1048101	Occurrence Severity	- n=87 patients with fractures of the distal radius; 96% female- Compared genotypes between those developing complex regional pain syndrome type I (CRPSI; n=15; mean age 62 years) and those that did not (Controls; n=72; mean age 65.6 years)	rs1048101 showed a significant association with the occurrence of CRPS I (p = 0.0176)
Hocking et al., 2010, United Kingdom	ADRB2	rs12654778	Occurrence (chronic widespread pain [CWP], non-chronic pain) - Severity - Pain status	- n=7083 individuals from the 1958 British Birth Cohort study; 50.4% female; 100% Caucasian	rs12654778 and rs1042713 were significantly associated with reduced risk of CWP (recessive minor allele model; p=0.02). Associated with pain status prior to correction of multiple testing (p=0.04).
		rs1042713			
		Haplotype rs12654778 rs1042713 rs1042714 rs1800888			Significantly predicted pain extent (p=0.003) and duration (p=0.002), and remained significant after correcting for gender, social class, psychological distress, and BMI.
Hwang et al., 2014, South Korea	SLC6A4	5-HTTLPR	Occurrence of Epigastric pain syndrome (EPS)	- n=381 Korean patients (n=112 functional dyspepsia patients; n=269 healthy controls)	S/S genotype was significantly associated with H. pylori-positive EPS patients (adjusted odds ratio (OR) 0.46; p = 0.048)..
	TRPV1	(945G>C)			C carrier and C/C genotype was significantly associated with EPS (adjusted OR 0.43; P = 0.033). After stratification, associations remained in H. pylori-positive EPS patients (adjusted OR 0.28; P = 0.025).
Jacobsen et al., 2012, Norway	COMT	rs4680	Severity	- n1=258 patients with lumbar disc herniation and sciatic pain; 47% female; mean age 41 years	Significant association between Met/Met genotype and increase in McGill sensory score (p=0.017). No clear association between VAS activity score and Met/Met versus Val/Val genotype (p=0.13). Significant

				- n2=249 pain-free controls matched on age, gender, and smoking status; 48% female; mean age 41 years All subjects European-Caucasian	associations between the COMT Met allele and two clinical measures (VAS activity score *p*=0.028, McGill sensory score *p*=0.023) at 6 months after inclusion
Janicki et al., 2006, USA	OPRM1	rs1799971	Severity	- n=121 patients with chronic pain and receiving long-term treatment with opioid analgesics - n=101 surgical patients undergoing elective laparoscopic abdominal surgery and opioid naïve (control group)	Frequency of the minor allele was approximately 50% lower in the chronic pain patients when compared to the opioid-naive acute postoperative group of patients without chronic pain (0.079 vs 0.158, *p*=0.009). No significant association between SNP and Pain.
Jensen et al., 2009, Sweden	COMT	rs4680	Severity	- n=43 healthy subjects; 72% female; mean age 26 years	No difference in pain ratings at baseline between genotypes. Significant main effect for genotype on repeated measures of pain stimuli (*p*=0.024). Met/met individuals reported significantly more pain compared to val/val (*p*=0.010).
Kambur et al., 2013, Finland	COMT	rs887200	Severity Pain toleration	- n=1000 female patients schedule for breast cancer surgery	Minor allele (C) carriers report significant less cold pain intensity (*p*<0.005).
		rs165774			Minor allele (A) carriers report significant less heat pain intensity (*p*=0.003).
Kolesnikov et al., 2013, Estonia	OPRM1	rs1799971	Occurrence Severity Duration	- n=102 patients undergoing lower abdominal surgery	Only chronic postsurgical pain patients carrying at least one copy of the G allele had higher pain intensity than A118A carriers (*p*=0.02).
Lintermans et al., 2016, Belgium	OPG	rs2073618 (G)	Severity	- n=245 breast cancer patients taking aromatase inhibitor (n=159; mean age 63 years) or	Carrying the G allele was associated with severity of musculoskeletal pain (*p*=0.018).

				tamoxifen (n=95; mean age 64 years)	
Liu et al., 2012, Taiwan	OPRM1	rs1799971	Severity	- n=96 patients with colon or rectum cancer (n=84) or stomach cancer (n=12) and experiencing oxiliplatin-induced painful neuropathy; 39% female; 70% ≥ 50 years old	Compared with the AA genotype (wild-type), patients with 118G allele variants (AG or GG) significantly reduced response to Ultracet. Pre- and post-treatment VAS scores for patients with G allele variants were 3.1 and 2.6, respectively; patients with AA genotype, pre- and post-treatment VAS scores were 3.0 and 0.9 (p<0.001). Patients with G allele variants had a higher percentage of moderate pain (VAS 4-6) after being treated with Ultracet (0 vs 15.2%; p=0.02)
Liu et al., 2014, Taiwan	TESPA1	rs2171497	Severity	- n=494 patients with ankylosing spondylitis (AS); 17% female; mean age 28.1 ± 9.7 years. - n=478 matched healthy controls; 17% female; mean age 27.3 ± 8.5 years. - Both groups were Han Chinese	Significant difference in VAS night pain scores between genotypes (p=0.040). Patients with the GG genotype had significantly worse VAS night pain scores than the CC genotype (31.49±18.07 vs 37.54±20.65, p=0.030) and CG genotype (31.49±18.07 vs 35.01±19.03, p=0.048).
Lotsch et al., 2009, Germany	COMT	rs4680	Sensitivity -cold pain threshold	- n=100 healthy volunteers	After controlling for the confounding FAAH rs4141964 variant, the difference between carriers of the COMT 472AA (n=10) and COMT 472GG (n=7) genotypes became significant (p=0.014), with carriers of the variant genotype being less cold pain–sensitive than non-

					carriers. No significant associations were found in the in vivo sample
Mao et al., 2011, USA	CYP19A1	rs60271534	Occurrence	- n=390 post-menopausal women with breast cancer and receiving an aromatase inhibitor; mean age 61.6 ± 9.9 years; 100% Caucasian.	Women carrying at least one 8-repeat allele had lower odds of aromatase inhibitor associated arthralgia (adjusted OR=0.41, 95% CI 0.21 to 0.79, *p*=0.008) after adjusting for demographic and clinical covariates.
McCann et al., 2012, USA	IL1R1	rs2110726	Occurrence Frequency Severity Distress	- n=398 women who are undergoing breast cancer surgery	Carriers of the minor allele were less likely to report breast pain prior to surgery (*p* = 0.007)
	IL13	rs1295686			Carriers of the minor allele were more likely to report breast pain prior to surgery (*p*= 0.019).
Meloto et al., 2015, USA	COMT	rs165774	Pain Threshold (Pressure pain Heat Pain)	2 independent cohorts including 100% Caucasian females: - n=200 temporomandibular disorder (TMD) - n=198 healthy controls	The minor A allele is associated with lesser pressure pain sensitivity (*p*=0.002, beta=-1.712, -2.782 <CI< -0.641). The A allele has protective effect against both risk of TMD (*p*=0.014, OR=0.81), and pressure pain sensitivity (*p*=0.001, beta=-0.880)
Nissenbaum et al., 2010, Israel	CACNG2	**Haplotype** rs4820242, rs2284015, rs2284017	Occurrence	- n=549 Jewish women with breast cancer who had undergone unilateral surgical removal of a breast; mean age 52.9 years; 60.4% Ashkenazi	Homozygous A-C-C haplotype significantly increased susceptibility to pain (OR=1.65, *p*= 0.001).
Ochroch et al., 2012, USA	OPRM1	Haplotype: rs679987 rs606148 rs59945 rs613341 rs616585	Severity	- n=90 thoracotomy patients	Haplotypes containing rs679987, rs606148, rs599945, rs613341, and rs616585 were associated with increased perioperative pain - Significant associations with 4 SNPs in OPRM1 (odds ratio, 95% confidence intervals): rs634479 (0.4, 0.17, 0.97), rs499796 (0.35, 0.13, 0.92), rs548646 (0.47, 0.23, 0.97), and rs679987 (0.1, 0.01, 0.84).
Oen et al., 2005, Canada	IL-6	rs1800795	Severity	- n=181 patients with juvenile rheumatoid	Genotype 174G/G was positively correlated with pain [regression

				arthritis; median age 3.7 years, range 0.3 to 15.8 years; 88.9% Caucasian	coefficient B=0.899, 95% confidence intervals (CI) 0.185, 1.612, *p*=0.014].
Omair et al., 2012, Norway	COMT	rs4680 rs4633	Severity	- n=93 patients chronic low back pain and lumbar disc degeneration; 62% female; age range 25-60 years	Association of rs4633 and rs4680 with post treatment improvement in VAS LBP (*p*=0.02, and *p*=0.02, respectively).
Potvin et al., 2009, Canada	DRD3	rs6280	Severity	- n1=37 Fibromyalgia (FM) patients; 89% female; mean age 50.6 ± 7.4 years. -n2=36 healthy controls; 81% female; mean age 47.9 ± 5.3 years	Genotype significantly predicted thermal pain in FM patients=0.038] but not in controls (*p*=0.505).
Rausch et al., 2012, USA	PTGS2	rs5277	Severity	- n=1149 lung cancer survivors enrolled in the May Clinic Lung Cancer Cohort; 47% female; mean age 65.2 ± 9.5 years; 100% Caucasian - Survival subgroups: <3 years (n=440); 3-5 years (n=354); >5 years (n=355).	In 5+ year lung cancer survivors, a SNP (rs5277) was associated with pain: carrying one or more minor (G) alleles reported greater pain scores (95% CI of OR=1.02-1.11).
	TNFA	rs1799964			In 5+ year lung cancer survivors, a SNP (rs1799964) was associated with pain: carrying one or more minor (G) alleles reported lower pain scores (95% CI of OR=0.92-0.98).
Reyes-Gibby et al., 2007, USA	IL-8	rs4073	Severity	- n=606 patients newly diagnosed with lung cancer; 74% White	rs4073 genotype (TT, 13%; TA + AA, 87%) significantly associated with severe pain among White patients (*p*=0.04).
Reyes-Gibby et al., 2009, USA	IL-8	rs4073	Severity	- n=156 newly diagnosed patients with pancreas cancer; non-Hispanic White	IL8-251T/A was a predictor for severe pain, with carriers of TT and AT genotypes having more than a threefold risk (OR 3.23, 95% CI 1.4, 4.7) for severe pain relative to the AA genotypes.

Reyes-Gibby et al., 2009, USA	TNF-alpha	rs1800629	Severity	- n=667 Caucasian lung cancer patients; 48% female; 48% ≤50 years old	Additive model for -308GA (rs1800629) (OR=1.67, 95% CI=1.08,2.58) was predictive of severe pain
Sery et al., 2006, Czech Republic	MAO-B	A/G polymorphism in intron 13	Severity	- n=284 patients undergoing tonsillectomy; 63% female; 100% Caucasian	Average intensity of postoperative pain in males with the G allele was significantly higher than males with A allele (p<0.03).
Solovieva et al., 2004, Finland	IL-1	- IL-1RN (G1812–A) - IL-1a(C889–T) - IL-1b(C3954–T)	Occurrence Severity Duration	- n=131 Finnish, middle aged men who are machine drivers, carpenters, or office workers	- Carriers of the IL-1RNA1812 allele had an increased risk of LBP (OR 2.5, 95% CI 1.0–6.0) and in combination with the IL-1aT889 or IL-1bT3954 allele had a higher risk (OR 2.0, 95%CI 0.8-4.9 of and more days with LBP than non-carriers. - Pain intensity was associated with the simultaneous carriage of the IL-1aT889 and IL-1RNA1812 alleles (OR 3.7, 95% CI 1.2–11.9). - Carriers of at least one copy of the IL-1bT3954 allele was associated with the number of days with pain.
Stephens et al., 2017, USA	TNF	rs1800610	Occurrence Severity	- n=410 women who underwent breast cancer surgery - 2 pain subgroups: No pain group (n=126; mean age 58.6 years; 73% White) and mild pain group (n=173; mean age 53.4; 63.7% White)	Patients who were heterozygous or homozygous for the rare T allele (i.e., CC versus CT + TT) were 63% less likely to be in the mild breast pain class (p=0.026).
	IL6	rs2069840			Rare G allele of rs2069840 decreases the risk for mild persistent breast pain after breast cancer surgery (p=0.005).
	CXCL8	rs4073			Patients homozygous for the rare A allele (i.e., TT + TA versus AA) were 60% less likely to be in the mild breast pain class (p=0.020).
Ulirsch et al., 2014, USA	FKBP5	rs2817038	Severity Interference	- n=948 European-American individuals within 24 hours after motor vehicle collision; 61% female	After adjustment for individual-level factors, living in more disadvantaged neighborhoods was associated with increased musculoskeletal pain (MSP) (p=0.0009) and increased pain interference with daily function

					(p<0.0001). The relationship between neighborhood disadvantage and MSP was moderated by SNP rs2817038.
Ursu et al., 2014, United Kingdom	P2RX7	rs208294	Severity	- n=159 patients with diabetic neuropathic pain; 40.2% female; mean age 62.6 years; 100% Caucasian	A trend of increased baseline average pain score was detected in female subjects with TT genotype versus the other genotypes (p=0.004)
		rs1718119			Females with AA genotypehad a 1.7 point covariate-adjusted higher mean baseline pain score than females with GG genotype (p=0.039)
Van Meurs et al., 2009, Netherlands	COMT	rs4680	Occurrence	- n=3033 Caucasian older adults with osteoarthritis and living in Rotterdam, The Netherlands; 57% female	Carriers of the 158Met variant had an almost 3-fold higher risk (p=0.02) of hip pain as compared with carriers of the Val/Val genotype.
Wei et al., 2016, Taiwan	BDNF	rs6265 (Val66Met)	severity	- 56 women with primary dysmenorrhea (PDM); mean age 23.1 ± 2.3 years - 60 healthy female controls; mean age 23.9 years - Both cohorts Chinese	Val/Val PDM subjects exhibited state-related negative correlations between pain rating index and PAG-seeded functional connectivity in them PFC (prefrontal cortex), dlPFC (dosal lateral prefrontal cortex), sensorimotor, secondary somatosensory cortex, and middle temporal gyrus (p<0.05).
Symptom cluster					

Illi et al, 2012, USA	IL4	rs2243248	Incidence Severity Distress	- 168 oncology outpatients - 85 family caregivers	Carrying the minor allele for IL4 rs2243248 (TG+GG) was associated with over a six fold increase in the odds of belonging to the "All high" class (OR: 6.02, 95% CI: 1.874, 19.366, *p*=0.003) along with younger age, being White, being a patient (vs a FC), having a lower functional status, and having a higher number of comorbid conditions
Doong et al., 2015, USA	IL-6	rs2069845		- n=398 - Female - Breast cancer before surgery	rs2069845 significantly associated with latent class membership (OR: 14.22, p = 0.013) while controlling for age, Karnofsky performance scale, living alone, and ethnicity.
	IL-13	rs1295686			rs1295686 significantly associated with latent class membership (OR: 28.53, p = 0.013) while controlling for age, Karnofsky performance scale, living alone, and ethnicity.
	TNF-α	rs1800610			rs1800610 significantly associated with latent class membership (OR: 4.97, p = 0.040) while controlling for age, Karnofsky performance scale, living alone, and ethnicity.

Abbreviations:
BPI: Brief Pain Inventory
CRPSI: Complex Regional Pain Syndrome Type 1
CWP: Chronic Widespread Pain
FC: Family Caregiver
FGID: Functional GI Disorders
HPS: High Pain Sensitive
LPS: Low Pain Sensitive
LBP: Low Back Pain
MSP: Musculoskeletal Pain
NRS: Numerical Rating Scale
PAG: Periaqueductal Gray
SA: Sexual Assault
SSS: Symptom Severity Scale

TMD: Temporomandibular Joint Dysfunction
TPT: Thermal Pain Thresholds
VAS: Visual Analog Scale

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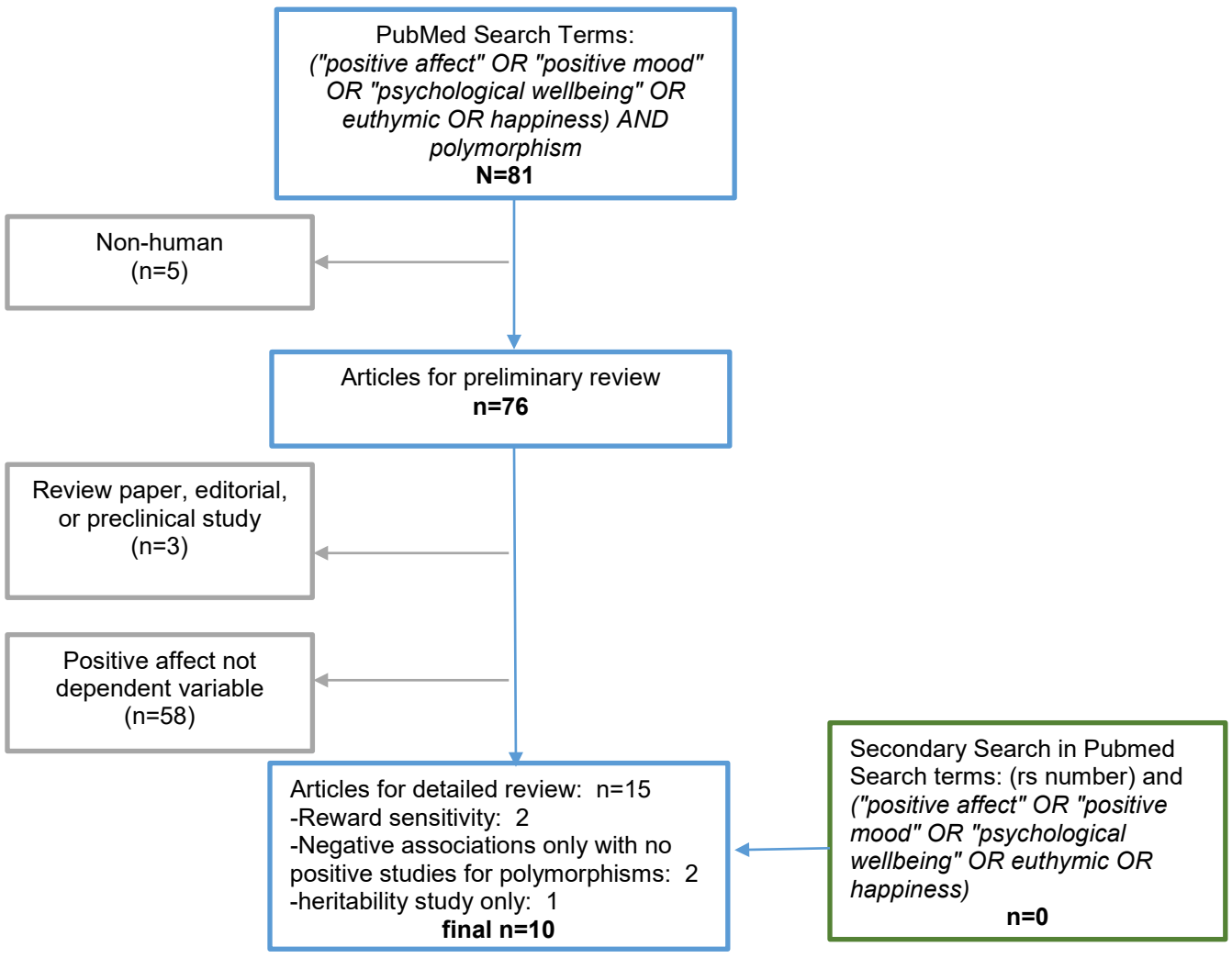
Supplemental Figure 6. Positive Affect Search Results



Symptom Definition: Positive affect is the opposite of negative affect and depressive symptoms. Synonyms include positive mood, psychological wellbeing, happiness and euthymia. Positive affect does not include pathological extremes, such as mania in bipolar disorder. It does not include reward sensitivity (i.e., pleasure after stimulation). Positive affect is measured using descriptors such as interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active (used in the Positive and Negative Affect Schedule instrument). As a National Institute of Nursing Research Common Data Element (CDE), it is conceptualized as “positive affect and wellbeing” and is measured as part of the “affective disturbance” aspect of affective symptoms to be an opposite for depression. Descriptors used in the CDE instrument include sense of well-being, hopeful, satisfying life, purposeful life, meaningful life, cheerful, worth, balance, and interest.

Methods: ("positive affect" OR "positive mood" OR "psychological wellbeing" OR euthymic OR happiness) AND polymorphism

Notes: Because positive affect had a small number of studies, polymorphism rather than “functional polymorphism” was used for the search. Of 81 English-language studies found using the search terms, 39 were <5 years old; however, all studies regardless of publication date were included in the flow chart above because of the small number. Two studies defined positive affect differently than the other studies, focusing on reward sensitivity, so they were not included. The studies with only negative associations included polymorphisms in DNMT1, DNMT3A, DNMT3B, MTHFR, KSR2, RAPGEF6, and LOC105377703; because no other studies showed positive associations for these genes, the articles were not included. One study estimated heritability but did not report on any specific polymorphisms, so it was not included. Happiness is closely related to positive affect. Its inclusion in the search argues for including synonymous search terms such as contentment. A search for (happiness OR contentment) AND polymorphism yielded no additional articles.

Supplemental Table 6. Evidence of Associations between Positive Affect and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Positive Affect Phenotype(s)	Sample	Relevant Findings
Bakker et al., 2014, Netherlands	BDNF CHRM2 DRD4 OPRM1	rs11030101 rs1824024 rs936461 rs495491 rs609148/rs648893	severity	n = 126 Dutch participants with previous depression with residual symptoms	PA did not differ by genotype before intervention; CHRM2 and OPRM1 variants increased PA for intervention (p<.01); BDNF and DRD4 variants maintained PA for intervention (p<0.01)
De Neve et al., 2011, United Kingdom	SLC6A4	short (S) or long (L) degenerative VNTR	severity	n = 2574 young adults from the National Longitudinal Study of Adolescent Health	L/L more likely to be satisfied with life than S/S (p<0.05)
Finan et al., 2010, USA	COMT OPRM1	rs4680 (val158met) rs1799971 (asn40asp)	severity	n = 46 females with fibromyalgia; mean age 53 ± 7.8 years; 93% Caucasian	PA did not differ overall by genotype; COMT met/met had decreased PA on high pain days (p<.05); OPRM1 asp carriers had steeper decline in PA on high pain days but increased PA overall (p<0.05)
Hartmann et al., 2014, Netherlands	SLC6A4	short (S) or long (L) degenerative VNTR; rs25531 rs25532	severity	n =361 Belgian female monozygotic twins; mean age 28 ± 7.5 years	Association between sleep quality and PA was stronger in carriers of at least one copy of the S allele (p<0.05)
Liu et al., 2017, China	COMT	rs4680 (val158met)	severity	n = 445 Chinese Han students; 75% female; mean age 24.3 ± 1.5 years	Met allele associated with decreased PA (p=0.019)
Lucht et al., 2009, Germany	OXTR	rs53576	severity	n = 289 German adults	Decreased PA in males homozygous for A allele (p<0.001)
Matsunaga et al., 2014, Japan	CNR1	rs806377	severity	n = 198 healthy Japanese students; 62% female; mean age 23.2 ± 0.4 years	Increased happiness for C allele carriers (p<0.05); increased positive mood for C allele carriers after intervention (p<0.05)
Moons et al., 2014, USA	OXTR	rs53576	severity	n = 172 students and staff affiliated with the University of California, Los Angeles; 60% female; mean age 21 years; 37% Asian American, 23% European American	No overall relationship between variant and PA; GG genotype associated with higher post social-stress PA in women with high levels of oxytocin
van Roekel et al., 2016, Netherlands	SLC6A4	short (S) or long (L) degenerative VNTR	severity	n = 269 adolescents; 58.4% female; mean age 14.2 years	S allele carriers had lower positive affect with poorer sleep (p=0.018)
Wingo et al., 2017, USA	LINC01221	rs322931	severity	n = 2522 African American adults in the Grady Trauma Project; 69% female; mean age 39.2 ± 13.7 years	Minor allele significantly associated with greater PA (p<0.001)

Abbreviations: PA: Positive affect; VNTR: Variable Number Tandem Repeat

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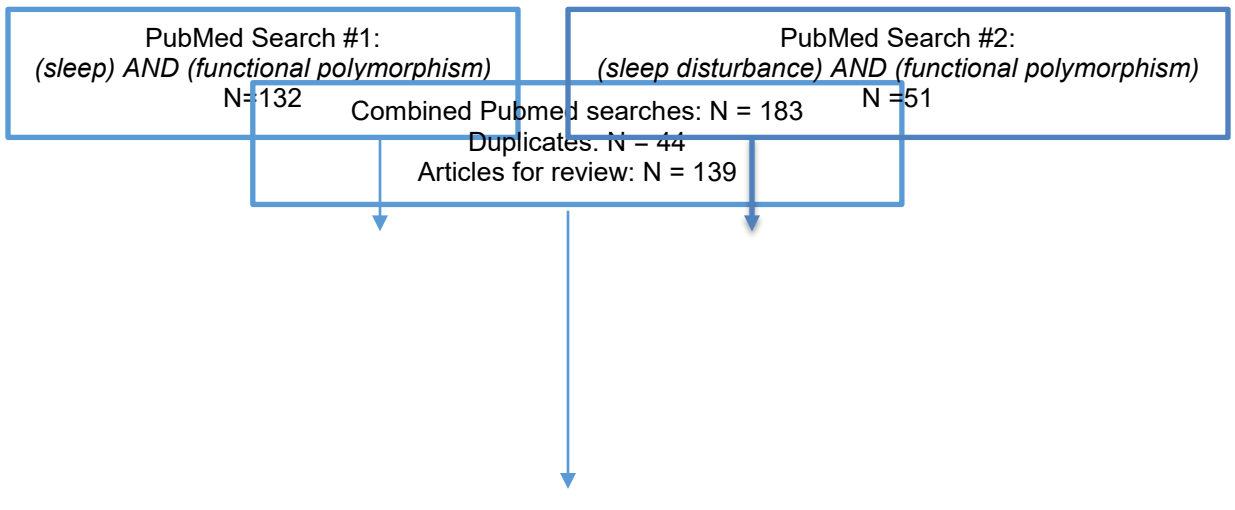
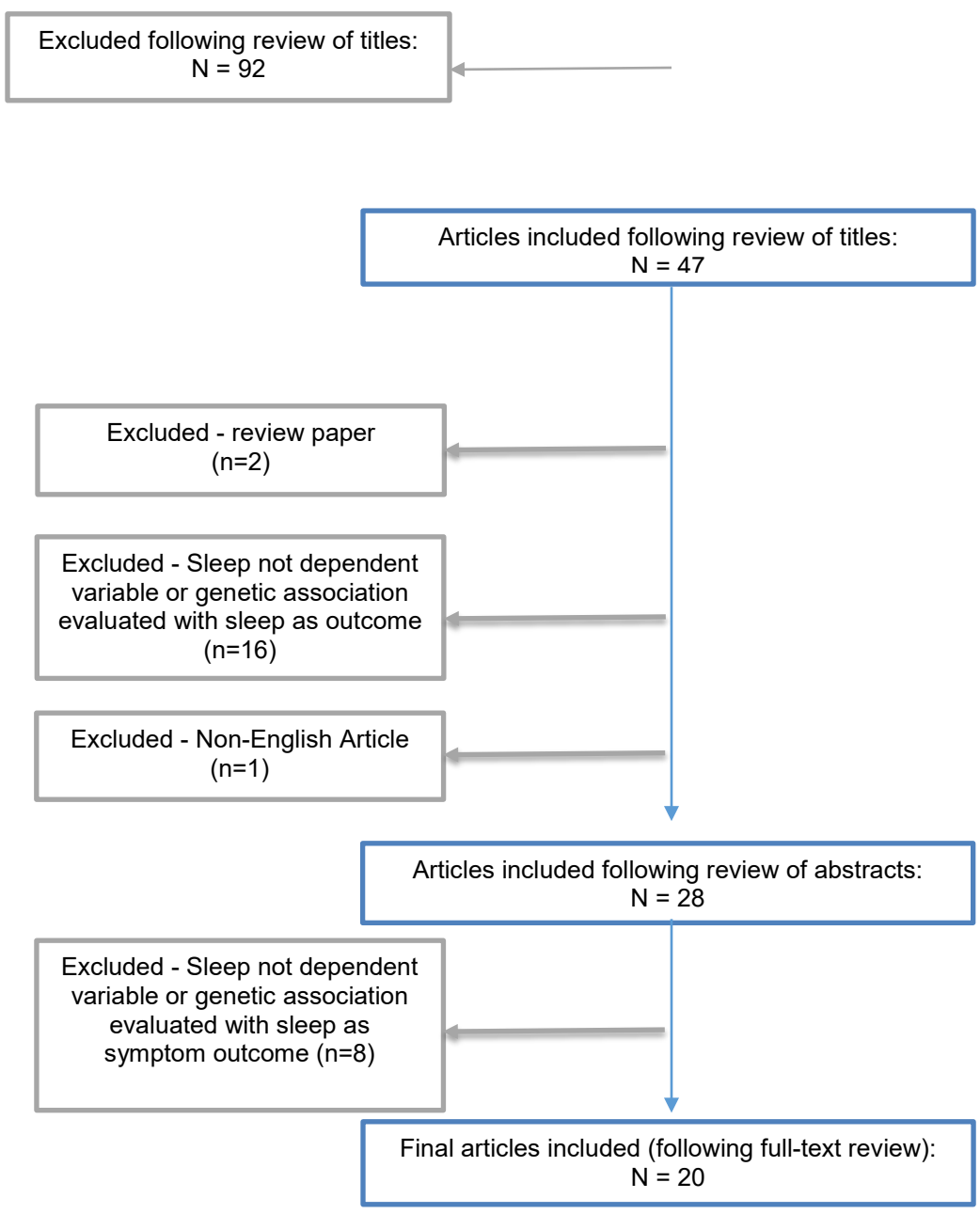
Supplemental Figure 7. Sleep Disturbance Search Results




Excluded following review of titles:
N = 92
Articles included following review of titles:
N = 47
Excluded - review paper
(n=2)
Excluded - Sleep not dependent variable or genetic association evaluated with sleep as outcome
(n=16)
Excluded - Non-English Article
(n=1)
Articles included following review of abstracts:
N = 28
Excluded - Sleep not dependent variable or genetic association evaluated with sleep as symptom outcome (n=8)
Final articles included (following full-text review):
N = 20

Supplemental Table 7. Evidence of Associations between Sleep Disturbance and Genetic Polymorphisms

Author, Year, Country	Gene	Polymorphism	Phenotype(s)	Sample	Relevant Findings
Alfaro et al., 2014, USA	IL1R2 IL-13 NFKB2	Haplotype A2: rs11674595[T] rs7570441[A] rs1800925 rs1056890	Sleep disturbance	- n = 398 women who underwent breast cancer surgery on one breast.	IL1R2 haplotype A2: Each additional dose of haplotype was associated with a 2.08-fold increase in the odds of belonging to the high sustained sleep disturbance class (*p*=.024). IL13 rs1800925: carrying one or two doses of the rare T allele (i.e., CC versus CT+TT) was associated with a 2.21-fold increase in the odds of belonging to the high sustained sleep disturbance class (*p*=.005). NFKB2 rs1056890: carrying one or two doses of the rare T allele (i.e., CC versus CT+TT) was associated with a 47% decrease in the odds of belonging to the high sustained sleep disturbance class (p=.028).
Amin et al., 2016, Netherlands	RBFOX3	rs9900428 rs9907432 rs7211029	Sleep latency	- meta-analysis - Discovery cohort: n = 4,242 subjects with European ancestry - Replication cohort: 12 independent cohorts (n = 30,377)	Variants (rs9900428, rs9907432 and rs7211029) were associated with sleep latency. Replicated findings in 12 independent populations (n = 30,377).
Aouizerat et al., 2009, USA	TNFA	rs1800629	Sleep disturbance	- N = 253 (168 patients with breast, prostate, lung and brain cancers; 85 family caregivers) - 53.8% female; mean age 61.4 ± 11.3 years; 74.6% White	Association with overall ratings of sleep disturbance and fatigue, and trajectories of these symptoms. Common allele homozygotes reported higher levels of sleep disturbance (*p* = .09) and morning fatigue (*p* = .02) than minor allele carriers.
Bachmann et al., 2012, Switzerland	ADA	rs73598374	Subjective sleepiness in response to sleep deprivation	Laboratory subgroup undergoing sleep deprivation: - n = 22 healthy volunteers prospectively matched by genotype (G/A and G/G – 11 people per genotype); mean age 24 years; 48%	Those with G/A genotypes reported significantly higher subjective sleepiness than those with the G/G genotypes during sleep deprivation (*p*<0.02).

				female; all Swiss or German	
Bachmann et al., 2012, Switzerland	BDNF	rs6265	subjective sleepiness	- N = 22 healthy volunteers equally representing 2 genotypes (i.e., val/val, val/met); 36% female; mean age 24 years - volunteers matched on age, sex, BMI, diurnal preference, ESS score, trait anxiety, and consumption of alcohol and caffeine - 4 nights in sleep laboratory	No differences in sleepiness between genotype groups. Val/val group had greater deep stage 4 sleep and NREM sleep intensity than val/met genotype.
Barclay et al., 2011, United Kingdom	SLC6A4	5HTTLPR (rs25531)	Sleep quality Diurnal preference	- N = 947 G1219 and G1219Twins longitudinal studies; 61.8% female; mean age 20.3 ± 1.8 years	Significant main effect of 5HTTLPR on sleep quality; L/L genotype associated with significantly poorer sleep quality (mean=6.35, SD=3.36) than carriers of at least one S allele (mean=5.67, SD=2.96; b= 0.34, *p*=0.005). No associations between PERIOD3 and CLOCK genes on sleep quality or diurnal preference.
Craig et al., 2006, United Kingdom	MAO-A	30 bp VNTR	Sleep disturbance	- N = 405 patients with Alzehiemer's disease; 31% female; mean age 78 years	MAO-A allele 4 associated with increased susceptibility to sleep disturbance (*p* = .008).
Doong et al., 2015, USA	IL-6 IL-13 TNFA	rs2069845 rs1295686 rs18800610	Symptom cluster including sleep disturbance	- N = 398 women prior to breast cancer surgery - Using LCPA, three distinct classes of patients were identified based on their experiences with the symptoms of pain, fatigue, sleep disturbance, and depression	Significant associations identified between rs2069845, rs1295686, and 18800610 and latent class membership.
Geoffroy et al., 2014, France	ASMT	rs4446909	Sleep quality	- N = 53 Caucasian adult subjects (n = 25 euthymic patients with bipolar	No association was observed between rs4446909 genotype and sleep quality (*p* = 0.37).

				disorder in remission and n = 28 healthy subjects)	
Gottlieb et al., 2015, USA	CBWD2	rs1191685 rs1823125 rs1807282 rs1964463	Sleep duration	- CHARGE Consortium GWAS - 18 population-based cohorts consisting of n = 47,180 individuals from European ancestry - Replication cohort: n = 4,771 African American individuals	CBWD2 polymorphisms associated with self-reported usual sleep duration. Association replicated in African American sample.
Hartmann et al., 2014, Netherlands	SLC6A4	5-HTTLPR (rs25531)	Sleep quality	- n = 361 Belgian adult female monozygotic twins; mean age 28 ± 7.5 years; 100% White	Significant interaction between sleep quality and genotype in predicting positive affect the next day: carriers of one (n=167) or two S-alleles (n=78) had a significantly steeper slope compared to LL carriers (n=116) ($\chi 2=4.16$, $p=.042$ and $\chi 2=3.90$, $p=.048$ respectively).
Illi et al., 2012	IL4	rs2243248	Symptom cluster including sleep disturbance	- N = 253 (i.e., 168 oncology outpatients and 85 family caregivers; 53.8% female - latent class profile analysis was used to identify distinct classes of symptom reports: Low Depression/Low Pain class; High Depression/Low Pain class; and All High class	rs2243248 associated with membership to the “all high” symptom class, controlling for age, being White, being a patient versus a caregiver, having functional status score, and having more comorbidities.
Jimenez et al., 2017, Colombia	COMT	rs4680	Sleep quality (i.e., satisfaction with sleep, insomnia, & hypersomnia)	- n = 270 university student in medical or nursing schools in Bogota, Colombia; 75.1% female; mean age 21.3 ± 3.8 years	Met carriers (Val/Met or Met/Met genotypes) had higher scores for hypersomnia (p = 0.001) and lower scores for mental health-related quality of life (p = 0.007), remained significant after correcting for multiple testing.
Maire et al., 2015, Switzerland	PER3	VNTR	Sleep quality, daytime sleepiness	- n = 28 healthy volunteers; 50% female; mean age 24.9 ± 3.3 years	No differences between PER3 genotypes and mean scores for Pittsburgh Sleep Quality Index or Epworth Sleepiness Scale at baseline.

Mansour et al., 2017, USA	PER3	rs1012477 rs10462021 rs11579477	Sleep quality	- n = 274 older adults; 64% female; mean age 73.4 ± 7.2 years	No significant associations between reports of sleep quality (e.g., sleep time, sleep latency) and polymorphisms; however nominally significant associations between rs1012477 and total CS score (p = 0.035); rs10462021 and rs1012477 and SRM (p = 0.017); rs228642 with total sleep time (p = 0.009); rs1012477 with sleep latency (SL).
Miaskowski et al., 2010, USA	IL-6	rs4719714	Sleep disturbance	- N = 288 (168 oncology outpatients and 85 family caregivers); 53.8% female; mean age 61.4 ±11.3 years	Common allele homozygotes reported higher levels of sleep disturbance than minor allele carriers (p = 0.003).
Ojeda et al., 2014, Colombia	MAOA	VNTR	Daytime sleepiness	- n = 210 university students living in Bogota, Colombia; 70% female; mean age 20.8 ± 2.7 years.	VNTR showed significant association with Epworth Sleepiness Scale (ESS) scores (p = 0.01): 3/3 genotype carriers had the lowest scores.
Perea et al., 2014, Colombia	PER3	rs57875989	Daytime sleepiness	- n = 294 healthy undergraduate university students in Colombia; 66.6% Female; mean age 20.5 ±2.7 years	No significant associations.
Retey et al., 2005, Switzerland	ADA	rs73598374	Sleep quality	N = 4,329; 47% female	No significant differences between genotype groups and scores for sleep time, efficiency, latency, or wakefulness after sleep onset (all p's > 0.05).
Spada et al., 2014, Germany	NPSR-1	rs324981	Sleep quality (sleep duraiong, rest duration, sleep onset, rest onset, & sleep latency)	N = 393 elderly subjects; 45% female; mean age 70.5 years ± 3.6 years; 100% White	Those with the homozygous T/T genotype had a significantly shorter sleep- and rest duration compared to subjects carrying the A-allele.

Abbreviations: Bipolar Disorder (BD); Composite Scale of Morningness (CSM); Epworth Sleepiness Scale (ESS); Family Caregivers (FC); General Sleep Disturbance Scale (GSDS); Karolinska Sleepiness Scale (KSS); Lee Fatigue Scale (LFS); Morningness-Eveningness Questionnaire (MEQ); Munich Chronotype Questionnaire (MCTQ); Neuropsychiatric Inventory with Caregiver Distress (NPI-D); Pittsburgh Sleep Quality Index (PSQI); Polysomnography (PSG); Stanford Sleepiness Scale (SSS); Working Memory (WM)

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