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Journal

American Journal of Geriatric Psychiatry, 22(10)

ISSN

1064-7481

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Publication Date

2014-10-01

DOI

10.1016/j.jagp.2014.03.009

Peer reviewed

Published in final edited form as:
Am J Geriatr Psychiatry. 2014 October ; 22(10): 997–1006.e5. doi:10.1016/j.jagp.2014.03.009.

Candidate SNP Associations of Optimism and Resilience in Older Adults: Exploratory Study of 935 Community-Dwelling Adults

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Abstract

Objective—Optimism and resilience promote health and well-being in older adults, and previous reports suggest that these traits are heritable. We examined the association of selected single-nucleotide polymorphisms (SNPs) with optimism and resilience in older adults.

Design—Candidate gene association study that was a follow-on at the University of California, San Diego sites of two NIH-funded multi-site longitudinal investigations: Women's Health Initiative (WHI) and SELenium and vitamin E Cancer prevention Trial (SELECT).

Participants—426 Women from WHI older than age 50, and 509 men older than age 55 (age 50 for African-American men) from SELECT.

Measurements—65 candidate gene SNPs that were judged by consensus, based on a literature review, as being related to predisposition to optimism and resilience, and 31 ancestry informative marker SNPs, genotyped from blood-based DNA samples and self-report scales for trait optimism, resilience, and depressive symptoms.

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Disclosures of Conflict of Interest: None of the authors has any disclosures of interest to report.

Results—Using a Bonferroni threshold for significant association (p=0.00089), there were no significant associations for individual SNPs with optimism or resilience in single-locus analyses. Exploratory multi-locus polygenic analyses with a p-value of <.05, showed an association of optimism with SNPs in MAO-A, IL10, and FGG genes, and an association of resilience with a SNP in MAO-A gene.

Conclusions—Correcting for Type I errors, there were no significant associations of optimism and resilience with specific gene SNPs in single-locus analyses. Positive psychological traits are likely to be genetically complex, with many loci having small effects contributing to phenotypic variation. Our exploratory multi-locus polygenic analyses suggest that larger sample sizes and complementary approaches involving methods such as sequence-based association studies, copy number variation analyses, and pathway-based analyses could be useful for better understanding the genetic basis of these positive psychological traits.

Keywords

Optimism; Resilience; Depression; Aging; Single-nucleotide polymorphisms; Genotyping

INTRODUCTION

Recent years have seen a growing interest in the medicine community for patient outcomes that go beyond symptom relief, such as well-being, as well as in positive psychological traits and their relationship with improved physical and mental health. Prominent among such traits are optimism and resilience, which have been reported to be associated with a lower risk of all-cause mortality in longitudinal studies of older adults (1;2). Yet, research into biological underpinnings of these domains is in very early stages.

Optimism reflects a disposition or tendency to expect good outcomes (3). Optimism has been studied in the context of a number of serious medical conditions and shown to be associated with less illness-related distress, higher quality of life and satisfaction, and lower incidence of depression (3). Optimistic older adults report higher levels of well-being and are more likely to engage in healthy behaviors than their pessimistic counterparts (4). A meta-analysis of 83 studies of optimism found a significant relationship between optimism and physical health outcomes including cardiovascular outcomes, physiological markers (including immune function), cancer outcomes, outcomes related to pregnancy, physical symptoms, pain, and mortality (each p<.001) (5). Two studies reported that low optimism was associated with increased loneliness and increased inflammation markers among older men (6;7). Findings regarding an association of optimism with cell immunity function have been mixed (8;9).

Resilience refers to positive adaptation to adversity or ability to recover readily from illness, depression, or adversity (10–12). It is associated with better health-related quality of life (13;14). A systematic review of studies of resilience among physically ill patients showed resilience to be associated with greater subjective well-being as well as with medically desirable behaviors or outcomes such as better self-care, treatment adherence, exercise adherence, and improved physical health (15).

Recent work suggests that both optimism and resilience are heritable (16), and share variation with positive states of mental health. One study reported that genetic variation in *CACNA1C* was related to lower levels of dispositional optimism as well as resilience (17). Another investigation found that variation in mineralo-corticoid haplotype was associated with dispositional optimism (18;19). Additionally, the *OXTR* gene, associated with oxytocin, impacted optimism and depression, and the influence of the gene on optimism mediated relationship to depression (19). The *OXTR* finding, however, was not replicated in the Nurses' Health Study sample (20).

Trait resilience level, as assessed by a self-report measure, was found to be heritable in a twin study (21). Although there have been few investigations of single nucleotide polymorphisms (SNPs) that may relate to trait resilience, a number of genes are thought to modulate adaptive responses to fear, and specifically, limbic and prefrontal cortex reactivity. Reported candidate genes for resilience include MAO-A, NYP, BDNF, CRHR1, FKBP5, 5-HTTLPR, COMT, and NGFI-A (22).

Most of the above mentioned studies employed samples with a broad range of ages, and it is unclear whether these SNPs may have the same associations in older adults as in younger people. Given that these traits seem particularly important to later-life outcomes, evaluation of the previously reported associations in older age samples could be fruitful. Indeed, there is some suggestion that certain SNP associations may attenuate with age. For example, an association of the “s” allele of the *5-HTTLPR* gene with reduced resilience reported in 423 undergraduate students (23) could not be replicated in older adults (24–26). In contrast to the much larger body of work on the genetic correlates of late-life neuropsychiatric disorders, especially dementias, only a few studies have investigated the genetics of positive psychological traits in older adults, (27).

In the present investigation, we assessed self-reported optimism and resilience in older adults, among whom the effects of stress could have accumulated because of aging. We examined associations of levels of these two traits with 65 candidate gene SNPs, which were culled from the literature based on their reported association with optimism or resilience as well as depression and common aging-related phenotypes (longevity, dementia, and anxiety). We hypothesized that, among older women and men, candidate gene SNPs would be associated with variation in levels of optimism and resilience. We also wished to explore the association of SNPs with severity of depressive symptoms, because depression may be considered as indicating a relative attenuation of these positive traits. The candidate gene approach has several well-known limitations (28–30). However, given the dearth of studies of genetic association of optimism and resilience in older adults, it is a reasonable first step toward beginning to understand the genetic underpinnings of positive psychological traits in the context of aging.

METHODS

Participants

Participants came from two large NIH-funded multi-site longitudinal investigations of older adults that were conducted at the University of California San Diego: Women's Health

Initiative (WHI) for women aged 50+, and SELenium and vitamin E Cancer prevention Trial (SELECT) for men aged 55+ (age 50+ among African-American men). Details of the methods for these investigations have been described previously (31;32). Briefly, at the time of enrollment, participants in the WHI were free of medical conditions commonly associated with shortened life expectancy (less than 3 years) or complicating conditions such as alcoholism or drug dependency. The SELECT study was a large 2×2 randomized controlled trial of selenium and Vitamin E, in which participants were free of prostate cancer at baseline.

A subsample of these participants consented to participate in follow-up studies focused on successful aging. In both studies the subjects completed an extensive self-report survey and provided blood samples. Some of the data from specific phenotypic measures (e.g., self-rated successful aging, depressive symptoms) have been published previously (33–36) but, to our knowledge, this is the first study to report genetic associations of positive psychological traits in subjects from the WHI and SELECT studies.

Participation in these studies was approved by the UCSD Human Subjects Protections Program. All the participants provided separate informed consent to participate in this follow-on investigation. A total of 1,152 WHI and SELECT participants for whom genomic DNA from whole blood was available were chosen for analyses.

Measures

Marital status, education, and self-reported ethnicity were obtained from data collected at the baseline (enrollment) visit, whereas current age was derived from the follow-on successful aging survey questionnaire. We employed commonly used published scales for optimism (Life Orientation Test or LOT (37)), resilience (25-item Connor-Davidson Resilience Scale or CD-RISC (38)), and depression (Center for Epidemiological Studies Depression Rating Scale or CES-D (39)).

The LOT (37) is a six-item measure of trait optimism with the following statements: “In unclear times, I usually expect the best”, “If something can go wrong for me, it will”, “I'm always optimistic about my future”, “I hardly ever expect things to go my way”, “I rarely count on good things happening to me”, “Overall, I expect more good things to happen to me than bad”. Responses are scored on a five-point Likert scale (“I agree a lot”, “I agree a little”, “I neither agree nor disagree”, “I disagree a little”, and “I disagree a lot”). Responses to “scored” items are coded such that high values imply greater optimism. This instrument has been evaluated in numerous studies, including some that included older adults (40) .

The CD-RISC (38) is a 25-item questionnaire which contains statements such as “I am in control of my life”, “I tend to bounce back after illness or hardship”, and “I am able to adapt to change”. Responses are rated on a five-item Likert scale (“Not true at all”; “Rarely true”; “Sometimes true”; “often true”; “True nearly all of the time”), and total scores range from 0 to 100, with higher scores reflecting greater resilience (38). The CD-RISC is reliable in older adults, is positively associated with health-related quality of life, and is negatively associated with severity of depression (38).

Candidate Gene SNP Selection

Candidate genes were selected by the investigators via a consensus process. We began by searching the PubMed and Google Scholar databases for relevant articles published before September 2011, using the following keywords and MeSH terms: [“SNP” or “mutation” or “genetic polymorphism” or “polymorphism” or “single nucleotide polymorphism” or “variation” or “variant”] and [“aging” or “successful aging” or “longevity” or “dementia” or “optimism” or “resilience” or “depression” or “anxiety”]. A manual search of relevant articles was also conducted. This yielded a list of 162 SNPs which were then prioritized by minor allele frequency to provide sufficient power to detect association in our study, evidence supported by published data, and biological relevance to our phenotypes of interest (optimism, resilience, and depression). The selected list of SNPs underwent assay design quality control filter for the Illumina GoldenGate custom assay on BeadXpress (Illumina; La Jolla, CA). The final list was comprised of 65 SNPs (Supplemental Table 1).

Genotyping

The Illumina 96-plex Golden Gate custom assay on BeadXpress (Illumina; San Diego, CA) was performed according to manufacturer's instructions at Expression Analysis Inc. (Durham, NC). Data quality analysis was performed with the dedicated Genome Studio software (Illumina, Inc.). Genotype data passed quality for 1,057 individuals. Among this set, 92 subjects were removed due to missing phenotype data. This left a total of 965 individuals for our analyses.

Global Ancestry Determination

Participants were predominately of self-reported European ancestry. However, given the possibility that at least a proportion of participants were admixed, we genotyped an additional 31 ancestry informative markers (AIMs) to discern ancestry for control of population stratification in our association analyses, using previously described methods (41–43). From the 965 subjects, 15 were excluded for poor genotyping of AIMs, 12 were predominately East Asian, 31 African, 8 Americas, and 899 Eurasian. Within the Eurasian group, 24 individuals were excluded due to significant admixture. After excluding these individuals, data from the remaining 875 subjects of predominately European ancestry were analyzed using multidimensional scaling (MDS) analysis implemented in PLINK (44) to correct for additional population stratification. The first three components from this analysis were used as covariates in all association analyses.

SNP Quality Control

Of the 65 candidate SNPs of interest, 9 were removed after applying quality control filters – i.e., minor allele frequency <0.01 (4 SNPs); missing genotypes in >0.1% of subjects (2 SNPs); and Hardy-Weinberg equilibrium exact p <0.0008 (4 SNPs). The total number of SNPs passing quality control was 56. Additionally, of the 875 individuals, 12 subjects were removed for having a SNP missingness rate of greater than 10%, leaving a total of 863 subjects.

Statistical Analyses

Single-locus tests of association were conducted using a linear regression model within the genetic analysis software PLINK (44). Additive, dominant, and recessive SNP main effects were tested for association with the three phenotypes of interest (optimism, resilience, and depression) as dependent variables, and gender, age, and genetic ancestry (three multidimensional scaling components) as covariates. Since our phenotypes of interest are complex and likely to be polygenic, we also conducted an exploratory polygenic analysis in which we included all the SNPs as independent variables in a regression model. For this analysis only, missing genotypes were imputed for all 56 candidate SNPs by calculating the mean allele value of each SNP across the sample (major allele=0, heterozygous=1, minor allele=2) and replacing any missing values with that number. We then conducted a stepwise regression analysis where in the first step, our covariates were simultaneously entered into the model, and in the second step, forward stepwise selection from among all 56 candidate SNPs was performed. We set the Bonferroni threshold for significant association ($p = .05/56 = .00089$) for our hypothesis-driven single-locus analysis. We also conducted Benjamini-Hochberg False Discovery Rate (FDR) (45) analysis for the single-locus associations, using the R Bioconductor 2.13 “multest” package (http://www.bioconductor.org/packages/release/bioc/html/multtest.html).

We analyzed data on men and women together as well as separately for the following reasons: (1) Gene-gender interactions have been reported in a number of genetic association studies for an array of traits (e.g., Rana et al., 2006 (46)). (2) Kendler and colleagues recently reported that risk factors for major depression vary between men and women (47). (3) Men and women were sampled from different cohorts (WHI and SELECT) that differed on several variables such as mean age.

RESULTS

Participants and Phenotypes

Demographic and phenotypic characteristics of the 403 women from WHI and 460 men from SELECT studies are summarized in Table 1. Levels of optimism and resilience were moderately positively correlated with each other (Pearson correlation, $r=0.450$, $p<0.001$). Severity of depressive symptoms correlated negatively with optimism (Pearson correlation, $r=-0.400$, $p<0.001$) and resilience (Pearson correlation, $r=-0.481$, $p<0.001$).

Single-Locus Association Analysis

Tables 2 and 3 present SNPs that showed the strongest statistical evidence of additive SNP main effects for optimism and resilience, respectively. For each SNP, the corresponding recessive and dominant model effects are also shown, as are results with the use of education as a covariate, and associations tested separately for women and men. The SNPs that showed the strongest statistical evidence of association in our primary analysis of each phenotype were rs1800896 in the interleukin-10 gene (*IL10*) for optimism (Table 2) and rs7412 in apolipoprotein A gene (*APOE)* for resilience (Table 3). No SNPs reached the Bonferroni statistical significance threshold ($p = .00089$) or reasonable FDR thresholds. The range of FDR was .55–1.0.

Exploratory Multi-locus Polygenic Association Analysis

Table 4 presents SNPs from our exploratory multi-locus polygenic analysis with a p-value of <.05. For optimism, the inclusion of three SNPs (rs6323, rs1800896, and rs1800792) in the monoamine oxidase A gene (*MAOA)*, *IL10*, and the fibrinogen G gene (*FGG*), respectively, showed the strongest statistical evidence of change in overall R^2 of the model. For resilience, the inclusion of one SNP (rs6323) in *MAOA* showed the strongest statistical evidence of change in overall R^2 of the model. For depression, the inclusion of one SNP (rs179973) in *CCKAR* showed the strongest statistical evidence of change in overall R^2 of the model.

Exploratory SNP × Age Interactions

Supplemental Tables 2 and 3 present the 10 SNPs with the strongest statistical evidence of association from SNP × age interaction analyses for the two positive psychological trait phenotypes of interest. Again, no SNPs reached the Bonferroni threshold of significance (p = .05/56 = .00089), with the exception of rs6314 in *PPP1R1B* for optimism (p=.0003). The SNP that showed the strongest evidence of a SNP × age interaction for resilience was rs7209436 in *CRHR1* (p=.01).

Exploratory SNP × Maternal Education Interactions

Supplemental Tables 4 and 5 present the top 10 SNPs from SNP × maternal education interaction analyses for optimism and resilience, respectively. Maternal education may reflect early childhood environment. Again, no SNPs reached the traditional genome-wide statistical significance threshold (1 × 10–8). SNPs that showed the strongest statistical evidence of a SNP × maternal education interaction for each of our three phenotypes were rs7103411 in BDNF for optimism (p=.04), and rs242940 in CRHR1 for resilience (p=.007).

Discussion

A large number of reports, including some longitudinal studies of all-cause mortality in older adults (1;2), have shown that these two traits appear to have a positive effect on survival that rivals or exceeds that of well-established health risk factors such as smoking, hypertension, obesity, and sedentary lifestyle (5). People in their 90s who endorsed higher levels of resilience had a 43% higher likelihood of living up to 100 years compared to their peers with lower resilience (48). In older adults, optimism and resilience have also been reported to be associated with better emotional health and self-rated successful aging (49), higher levels of well-being, and greater engagement in healthy behaviors (4). Many older adults consider the ability to adapt to circumstances and positive attitude toward the future as being more important to their well-being than an absence of physical disease and disability (50;51). Yet, there is a dearth of investigations of genetic associations of these positive psychological traits, particularly in older adults. Understanding their genetic underpinnings could potentially lead to the development of interventions to enhance the levels of these and other protective factors related to health and well-being in old age which is typically characterized by diseases and disability.

Our investigation has several strengths. From a phenotypic perspective, we assessed optimism, resilience, and depression using standardized rating scales. We selected high-probability candidate genes based on prior literature that had largely included younger samples, performed thorough genetic ancestry analysis, applied conservative quality control procedures, and employed a Bonferroni threshold for determining significant association ($p=0.00089$) for statistical significance of our hypothesis-based single-locus analyses. The study also had important limitations. From a genetics perspective, it was underpowered, limiting our ability to detect small effects. This was also a cross-sectional investigation with selected phenotypic and genotypic measures in a sample that may not be fully representative of the entire population of older adults.

Correcting for Type I errors, we found no statistically significant results using single-locus association analyses or exploratory multi-locus polygenic analysis. This failure to identify significant associations does not necessarily mean that such associations do not exist. Positive psychological traits are likely to be genetically complex, with many loci with small effects contributing to phenotypic variation. In addition, although our strategy of selecting high-probability candidate genes was scientifically justifiable, it is noteworthy that many genetic variants identified by genome-wide association studies have not emerged from lists of “usual suspects” and have included genes previously not thought to be involved in the target disease etiology (52).

In the exploratory multi-locus polygenic analyses, not correcting for type I errors, the MAOA SNP rs6323 showed possible association with both optimism and resilience. MAOA deaminates several key neurotransmitters including dopamine, epinephrine, norepinipherine, and serotonin. Variation in MAOA has been associated with aggression and impulsivity in several reports (53). MAOA has also been investigated in the context of early brain maturation, such that individuals with high-activity MAOA alleles are less likely to develop psychopathology in the context of childhood maltreatment (53). In our sample, resilience showed possible association with IL10, an anti-inflammatory cytokine as well as FGG. Previously, higher levels of “vigor”, a trait that overlaps with resilience, have been reported to be associated with lower levels of fibrinogen (54), and IL10 has been associated with protection of the immune system in later life (55). Nonetheless, the results of our multi-locus analyses are only tentative, and have value primarily as a proof of concept. They need to be replicated using larger samples.

There is also a need for additional analytic approaches to detect genotypic associations of optimism and resilience. As we better appreciate the nature of diverse individual differences in trait characteristics, it will be useful to make better use of empirically derived phenotype selection criteria that integrate neural systems information with self-reported behavioral data. From a genotyping perspective, complementary approaches exist such as genome-wide association scans (52), variations via sequencing studies (56), analysis of copy number variations (57), accommodation and consideration of epigenomic factors (58), and more sophisticated multi-locus analyses.

It is also possible that there are real differences in SNP associations between younger and older subjects. Data show that, with aging, there is a reduction in bio-behavioral response to

negative emotional stimuli (59). This is, however, typically not accompanied by an increase in levels of resilience on assessment scales (35). For example, it has been suggested that age-related depletions in the serotonergic neurotransmitter efficiency may reduce differences between the impact of “s” and “l” alleles of the *5-HTTLPR* gene (24;26;60). Another possibility is that of “survivor bias”, which can be problematic in cross-sectional studies. Also, the specific inclusion-exclusion criteria for the two study samples (WHI and SELECT) might restrict generalizability of the findings to other populations, e.g., older adults with common medical problems such as hypertension. The influence of lifespan changes in the phenotypes as well as selection of survivors could be controlled for in a longitudinal population-based design.

We hope that this study could open up new research avenues because of its focus on genetics of positive personality traits that are reportedly associated with better overall health and longevity. Furthermore, traits such as resilience are potentially amenable to intervention, as resilience training was found to be effective in a pilot study among breast cancer survivors (61). The potential value of genotyping research as represented in the present study is that it may point toward personalized interventions that could prevent or mitigate development of psychopathology and even physical morbidity. Understanding the circumstances and lifespan differences in the influence of genes on these protective phenotypes is a starting point in this line of investigation. Future studies with larger sample sizes and different genotyping techniques are required to carefully characterize the interplay among genes, positive psychological traits, and health status across the lifespan. Such research will constitute one of the major components of the scientific basis underlying the proposed new model of Positive Psychiatry of Aging (62).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported, in part, by National Institutes of Health grants T32 MH019934, P30MH066248, K01DK087813, 1K01AG035031, and NCRS UL1RR031980, by the John A. Hartford Foundation, and by the Sam and Rose Stein Institute for Research on Aging. We also wish to acknowledge the special help with data management provided by Rebecca Daly, and administrative assistance by Sandra Dorsey.

The Women's Health Initiative (WHI) program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. We wish to specifically acknowledge WHI investigators, especially the ones listed in https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.

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Table 1

Comparison of Demographic and Phenotvpic Characteristics of the Two Subject Groups

	N	WHI	N	SELECT	p-value
Age in years (Median, Range)	403	73.0 (58–89)	458	64.0 (56–89)	<0.001[a]
Gender (%Female)	403	100.0	460	0.0	--
Education (Median)	400	Some college/Associate Degree	340	College graduate/Baccalaureate Degree	<0.001[a]
Mother's years of education (Median)	335	12.0 (3.5)	423	12.0 (2.8)	.137[a]
Father's years of education (Median)	331	12.0 (4.1)	414	12.0 (3.6)	.157[a]
Annual Income (Median)	401	$35,000–49,000	335	$75,000–99,999	<0.001[a]
Ethnicity (% Caucasian)	398	78.4	460	97.4	<0.001[b]
Marital status (% Married)	402	60.4	445	80.0	<0.001[b]
Phenotypes					
Optimism: LOT Total score (Median, SD)	393	24.0 (3.1)	448	24.0 (3.2)	<0.001[a]
Resilience: CD-RISC Total score (Median, SD)	323	77.0(12.3)	409	78.0(12.0)	.009[a]
Depression: CES-D Total score (Median, SD)	332	4.0 (6.2)	407	4.0 (6.0)	.049[a]

Note:

LOT = Life Orientation Test (37)

CD-RISC = Connor-Davidson Resilience Scale (38)

CES-D = Center for Epidemiological Studies Depression Rating Scale (39)

[a] Mann Whitney U-Test

[b] Chi-Square

[c] Independent T-Test

Table 2

Sinqle-Locus SNP Effects on Optimism

SNP	Gene	Base Pair	N	Beta	Additive P	Dominant P	Recessive P	N	Beta	Additive P*	N	Beta	Females P	N	Beta	Males P
rs1800896	*IL10*	206946897	851	−0.421	**0.009**	**0.012**	0.087	732	−0.265	0.119	401	−0.564	**0.014**	450	−0.300	0.179
rs1800497	*DRD2/ANKK1*	113270828	848	0.432	**0.034**	0.130	**0.010**	729	0.453	**0.036**	398	0.015	0.960	450	0.773	**0.006**
rs1800792	*FGG*	155534408	849	0.321	**0.040**	**0.033**	0.256	730	0.255	0.129	399	0.282	0.213	450	0.370	0.087
rs363039	*SNAP25*	10220496	839	0.279	0.085	0.057	0.508	720	0.199	0.248	390	0.044	0.848	449	0.488	**0.033**
rs3758391	*SIRT1*	69643342	850	0.281	0.085	0.053	0.558	731	0.326	0.060	400	0.301	0.178	450	0.236	0.324
rs179973	*CCKAR*	16362388	851	0.306	0.093	0.082	0.554	732	0.210	0.275	401	0.528	**0.049**	450	0.155	0.533
rs662	*PON1*	94937446	850	−0.271	0.096	**0.012**	0.631	731	−0.260	0.131	401	−0.633	**0.006**	449	0.096	0.677
rs2061174	*CHRNA7*	136661400	851	0.267	0.105	0.172	0.201	732	0.336	0.053	401	0.392	0.102	450	0.129	0.569
rs1205	*CRP*	159682233	851	−0.241	0.143	0.134	0.473	732	−0.304	0.081	401	−0.247	0.285	450	−0.219	0.350
rs2070592	*PYY*	42031331	844	−0.222	0.170	0.127	0.600	725	−0.239	0.160	394	−0.281	0.203	450	−0.136	0.565

Note: p-values are based on single locus association analysis using a linear regression model. Additive, dominant, and recessive SNP main effects were tested for association with Life Orientation Test score for optimism as the dependent variable, and gender, age, and genetic ancestry (three multidimensional scaling components) as covariates. Education was also added as a covariate.

Table 3

Sinqle-Locus SNP Effects on Resilience

SNP	Gene	Base Pair	N	Beta	Additive P	Dominant P	Recessive P	N	Beta	Additive P*	N	Beta	Females P	N	Beta	\Males P
rs7412	*ApoE4*	45412079	710	−2.264	**0.050**	0.097	0.058	605	−1.776	0.151	307	−4.645	**0.007**	403	−0.174	0.912
rs1360780	*FKBP5*	35607571	740	−1.158	0.088	**0.021**	0.922	633	−1.278	0.082	329	0.197	0.851	411	−2.292	**0.010**
rs429358	*ApoE4*	45411941	703	1.551	0.103	0.064	0.770	596	1.686	0.107	295	2.298	0.111	408	0.806	0.527
rs162431	*PYY*	42030175	726	−1.963	0.169	0.147	0.856	620	−2.132	0.159	323	−3.246	0.089	403	−0.171	0.938
rs324650	*CHRM2*	136693661	741	0.809	0.188	0.563	0.101	634	0.726	0.275	330	0.768	0.407	411	0.705	0.392
rs2070592	*PYY*	42031331	734	−0.874	0.193	0.112	0.805	627	−0.809	0.258	323	−0.195	0.842	411	−1.391	0.133
rs8191992	*CHRM2*	136701308	741	0.820	0.200	0.234	0.381	634	0.820	0.242	330	0.880	0.377	411	0.762	0.362
rs3745833	*GALP*	56693620	738	0.831	0.223	0.908	**0.017**	631	0.916	0.211	328	1.736	0.085	410	−0.046	0.961
rs1800629	*TNF-alpha*	31543031	725	0.946	0.283	0.311	0.558	619	1.058	0.269	322	1.429	0.304	403	0.525	0.645
rs1800908	*CCKAR*	26492222	741	−2.151	0.289	0.289	NA	634	−1.603	0.452	330	−1.898	0.505	411	−2.059	0.479

Note: p-values are based on single locus association analysis using a linear regression model. Additive, dominant, and recessive SNP main effects were tested for association with Connor-Davidson Resilience Scale score for resilience as the dependent variable, and gender, age, and genetic ancestry (three multidimensional scaling components) as covariates. Education was also added as a covariate.

Table 4

Multi-locus Polvgenic Analyses

Dependent Variable	N	SNP	Gene	Forward Stepwise Beta	Forward Stepwise p	Overall Change R^2	Change R^2 p
Optimism (Life Orientation Test-Revised)	840	rs1800896	*IL10*	−0.090	0.008	0.005	0.047
		rs6323	*MAOA*	−0.074	0.030		
		rs1800792	*FGG*	0.068	0.047		
Connor Davidson Resilience Scale	731	rs6323	*MAOA*	−0.086	0.020	0.007	0.020
Center for Epidemiological Studies Depression Scale	739	rs179973	*CCKAR*	−0.084	0.023	0.007	0.023

Note: None of the SNP associations reached Bonferroni-corrected siqnificance level of p=.00089.