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

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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 years, and 509 men older than age 55 years (age 50 years 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.* **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 multilocus polygenic analyses with $p < 0.05$ showed an association of optimism with SNPs in MAOA, IL10, and FGG genes, and an association of resilience with a SNP in MAOA 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 multilocus polygenic analyses suggest that larger sample sizes and complementary*

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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. (Am J Geriatr Psychiatry 2014; 22:997–1006)

Key Words: Optimism, resilience, depression, aging, single-nucleotide polymorphisms, genotyping

Recent years have seen a growing interest in the medical community for patient outcomes that go beyond symptom relief, such as well-being, as well as the identification of 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 $p < 0.001$).[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 *MAOA, NYP, BDNF, CRHR1, FKBP5, 5-HTTLPR, COMT, and NGFI-A*.[22]

Most of these studies included 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] Given the dearth of studies of genetic association of optimism and resilience in older adults, however, it is a reasonable first step toward understanding the genetic underpinnings of positive psychological traits in the context of aging.

METHODS

Participants

Participants came from two large U.S. National Institutes of Health–funded multi-site longitudinal investigations of older adults that were conducted at the University of California, San Diego: the Women's Health Initiative (WHI) for women aged 50 years and older, and the SELenium and vitamin E Cancer prevention Trial (SELECT) for men aged 55 years and older (age 50 years and older 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 University of California, San Diego, 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, and current age was derived from the follow-on successful aging survey questionnaire. We employed commonly used published scales for optimism (Life Orientation Test [LOT][37]), resilience (25-item Connor-Davidson Resilience Scale [CD-RISC][38]), and depression (Center for Epidemiological Studies Depression Rating Scale [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 that 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, Inc.; La Jolla, CA). The final list comprised 65 SNPs (Supplemental Table 1; available online).

Genotyping

The Illumina, Inc., 96-plex Golden Gate custom assay on BeadXpress 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. Given the possibility that at least a proportion of participants were admixed, however, 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 Native American, 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 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—namely, minor allele frequency less than 0.01 (4 SNPs); missing genotypes in greater than 0.1% of subjects (2 SNPs); and Hardy-Weinberg equilibrium exact p less than 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 sex, age, and genetic ancestry (three multidimensional scaling components) as covariates. Because 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

TABLE 1. Comparison of Demographic and Phenotypic Characteristics of the Two Subject Groups

	N	WHI	N	SELECT	p
Age in years (Median, Range)	403	73.0 (58–89)	458	64.0 (56–89)	<0.001[a]
Sex (% 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)	0.137[a]
Father's years of education (Median)	331	12.0 (4.1)	414	12.0 (3.6)	0.157[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)	0.009[a]
Depression: CES-D Total score (Median, SD)	332	4.0 (6.2)	407	4.0 (6.0)	0.049[a]

Notes: 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]χ^2 test.

Bonferroni threshold for significant association ($p = 0.05/56 = 0.00089$) 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.[46]); 2) Kendler et al.[47] recently reported that risk factors for major depression vary between men and women; and 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 ($p = 0.00089$) or reasonable FDR thresholds. The range of FDR was 0.55–1.0.

Exploratory Multi-locus Polygenic Association Analysis

Table 4 presents SNPs from our exploratory multi-locus polygenic analysis with a p-value of less than 0.05. 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

TABLE 2. Single-locus SNP Effects on Optimism

SNP	Gene	Base Pair	N	Beta	Additive p	Dominant p	Recessive p	N	Beta	Additive p[a]	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

Notes: 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 sex, age, and genetic ancestry (three multidimensional scaling components) as covariates. Significant p values are in bold.

[a]Education was added as a covariate.

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 (available online) 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 ($p = 0.05/56 = 0.00089$), with the exception of rs6314 in *PPP1R1B* for optimism ($p = 0.0003$). The SNP that showed the strongest evidence of a SNP × age interaction for resilience was rs7209436 in *CRHR1* ($p = 0.01$).

Exploratory SNP × Maternal Education Interactions

Supplemental Tables 4 and 5 (available online) 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 ($p = 0.04$), and rs242940 in CRHR1 for resilience ($p = 0.007$).

DISCUSSION

A large number of reports, including some longitudinal studies of all-cause mortality in older adults,[1,2] have shown that optimism and resilience 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 nineties who endorsed higher levels of resilience had a 43% higher likelihood of living up to 100 years compared with their peers with lower resilience.[48] In older adults, optimism and

TABLE 3. Single-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

Notes: 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 sex, age, and genetic ancestry (three multidimensional scaling components) as covariates. Education was also added as a covariate.

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 utilized 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

TABLE 4. Multi-locus Polygenic 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

Notes: None of the SNP associations reached Bonferroni-corrected significance level of p = 0.00089.

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 typically not accompanied by an increase in levels of resilience on assessment scales, however.[35] For example, it has been suggested that age-related depletions in 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 can 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]

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SUPPLEMENTAL TABLE 1. Candidate SNPs and Ancestry Informative Markers Included in the Present Study

Gene	Locus Name	Chromosome	Coordinate
ADRB2 1	rs1042713	5	1.48E+08
ADRB2 2	rs10497191	2	1.59E+08
APOE	rs449647	19	45408564
ApoE4 1	rs429358	19	45411941
ApoE4 2	rs7412	19	45412079
APP 1	rs78280744	21	27253998
APP 2	rs2830102	21	27535027
BDNF 1	rs7103411	11	27700125
BDNF 2	rs6265	11	27679916
CCKAR 1	rs1799752	17	61565890
CCKAR 2	rs1800908	4	26492222
CETP	rs5882	16	57016092
CHRM2 1	rs324650	7	1.37E+08
CHRM2 2	rs8191992	7	1.37E+08
CHRNA7	rs2061174	7	1.37E+08
CLOCK	rs534654	4	56290220
COMT	rs4680	22	19951271
CRHR1 1	rs242940	17	43892600
CRHR1 2	rs7209436	17	43870142
CRP	rs12474609	2	1.42E+08
CTSD	rs179973	6	16362388
DBH 1	rs1131497	11	1.22E+08
DBH 2	rs16147	7	24323410
DISC1	rs821616	1	2.32E+08
DRD2/ANKK1	rs1800497	11	1.13E+08
DRD3	rs6280	3	1.14E+08
FGG	rs1800792	4	1.56E+08
FKBP12	rs6041759	20	1352322
FKBP5	rs1554948	17	7286326
FOXO3A	rs2802	19	58315273
GAB2	rs10877030	12	58256714
GALP	rs3745833	19	56693620
GWA_14q32.13	rs11725412	4	38277754
HOMER1	rs6871510	5	78792344
Hsp70	rs2227956	6	31778272
IL10	rs1800896	1	2.07E+08
IL1B	rs17070145	5	1.68E+08
IL-6	rs1800795	7	22766645
LOC651924	rs6907175	6	1.42E+08
LRP1B	rs12498138	3	1.21E+08
MAOA	rs6323	X	43591036
MAOB	rs10793294	11	77996403
MINPP1	rs9664222	10	89338633
MORF4	rs34402795	4	1.75E+08
MTHFR	rs1801133	1	11856378
NPY	rs162431	17	42030175
NR3C1	rs6190	5	1.43E+08
PGBD1	rs3800324	6	28264681
PON1 1	rs662	7	94937446
PON1 2	rs2760118	6	24503590
PPARG 1	rs1805192	3	12421238
PPARG 2	rs1801282	3	12393125
PPP1R1B	rs6314	13	47409034
PRNP	rs1799990	20	4680251
PYY 1	rs16944	2	1.14E+08
PYY 2	rs2070592	17	42031331
SIRT1	rs3758391	10	69643342
SNAP25	rs363039	20	10220496
SNAP25	rs3794712	17	37791487
SORL1	rs11622883	14	95155776
TGFB1	rs1800468	19	41860587
TNF-alpha	rs1800629	6	31543031
TNK1	rs1557553	22	44760984
WRN	rs2725335	8	30892513
WWC1 (KIBRA)	rs17571	11	1782594
AIMS 1	rs10079352	5	1.17E+08
AIMS 10	rs2024566	22	41697338
AIMS 11	rs2166624	13	42579985
AIMS 12	rs2196051	8	1.22E+08
AIMS 13	rs2593595	17	41056245
AIMS 14	rs2717329	7	19062775
AIMS 15	rs3098610	2	2.33E+08
AIMS 16	rs310644	20	62159504
AIMS 17	rs3823159	6	1.36E+08
AIMS 18	rs4471745	17	53568884
AIMS 19	rs4664511	2	1.53E+08
AIMS 2	rs10521432	X	43633740
AIMS 20	rs4705360	5	1.49E+08
AIMS 21	rs4833103	4	38815502
AIMS 22	rs4907251	2	97484814
AIMS 23	rs4918664	10	94921065
AIMS 24	rs6737672	2	1.59E+08
AIMS 25	rs6990312	8	1.11E+08
AIMS 26	rs7251928	19	4077096
AIMS 27	rs734241	10	1.15E+08
AIMS 28	rs7722456	5	1.7E+08
AIMS 29	rs7837234	8	64220654
AIMS 3	rs1108580	9	1.37E+08
AIMS 30	rs842639	2	61095245
AIMS 31	rs9880567	3	22376894
AIMS 4	rs1205	1	1.6E+08
AIMS 5	rs12878166	14	74250715
AIMS 6	rs1360780	6	35607571
AIMS 7	rs1611115	9	1.37E+08
AIMS 8	rs1834640	15	48392165
AIMS 9	rs1863086	2	1.55E+08

SUPPLEMENTAL TABLE 2. SNP × Age Interactions for Optimism

SNP	Gene	Chromosome	Base Pair	N	Beta	SNPxAge p
rs6314	*PPP1R1B*	13	47409034	838	0.1244	**0.0003285**
rs1800497	*DRD2/ANKK1*	11	113270828	848	−0.07496	**0.003382**
rs662	*PON1*	7	94937446	850	−0.04392	**0.03579**
rs1360780	*FKBP5*	6	35607571	851	0.03995	0.05696
rs1554948	*TNK1*	17	7286326	845	−0.03749	0.05781
rs6871510	*HOMER1*	5	78792344	851	−0.04417	0.05836
rs1800795	*IL-6*	7	22766645	848	−0.03598	0.06872
rs17571	*CTSD*	11	1782594	848	−0.05383	0.08335
rs12474609	*LRP1B*	2	141721142	850	−0.04	0.1332
rs162431	*PYY*	17	42030175	831	−0.05942	0.1394
rs1800896	IL10	1	206946897	851	−0.02982	0.1517
rs2725335	WRN	8	30892513	849	−0.0587	0.1826
rs4680	COMT	22	19951271	848	0.02719	0.1921
rs179973	CCKAR_1	6	16362388	851	−0.03119	0.1994
rs1800908	CCKAR_2	4	26492222	851	0.08246	0.2128
rs2061174	CHRNA7	7	136661400	851	0.0255	0.232
rs429358	ApoE4_1	19	45411941	807	−0.03525	0.2367
rs17070145	WWC1 (KIBRA)	5	167845791	851	0.02491	0.2516
rs1042714	ADRB2_2	5	148206473	842	−0.02198	0.2826
rs7412	ApoE4_2	19	45412079	817	0.03124	0.3284
rs1800792	FGG	4	155534408	849	−0.01913	0.3358
rs3800324	PGBD1	6	28264681	849	0.0414	0.3876
rs2760118	PON1_2	6	24503590	851	0.01663	0.4511
rs1205	CRP	1	159682233	851	−0.01471	0.4936
rs10793294	GAB2	11	77996403	851	−0.01612	0.5101
rs11622883	GWA_14q32.13	14	95155776	847	−0.01313	0.5241
rs2070592	PYY_2	17	42031331	844	−0.013	0.5535
rs7209436	CRHR1_2	17	43870142	844	0.01127	0.5727
rs1799990	PRNP	20	4680251	839	0.01073	0.609
rs821616	DISC1	1	232144598	851	0.01071	0.611
rs1131497	SORL1	11	121502745	851	0.01033	0.6153
rs363039	SNAP25	20	10220496	839	−0.0101	0.6285
rs9664222	MINPP1	10	89338633	845	−0.01142	0.6472
rs2227956	Hsp70	6	31778272	845	−0.01164	0.6536
rs7103411	BDNF_1	11	27700125	845	0.01021	0.6729
rs5882	CETP	16	57016092	849	−0.00736	0.7096
rs6280	DRD3	3	113890815	849	0.00785	0.7097
rs1801133	MTHFR	1	11856378	848	0.007416	0.7241
rs6265	BDNF_2	11	27679916	846	0.009027	0.7259
rs242940	CRHR1_1	17	43892600	847	−0.00654	0.7335
rs534654	CLOCK	4	56290220	850	0.006025	0.8031
rs1108580	DBH_1	9	136505114	841	−0.004606	0.8223
rs1800629	TNF-alpha	6	31543031	831	−0.006002	0.8333
rs3758391	SIRT1	10	69643342	850	0.004334	0.8401
rs16944	IL1B	2	113594867	830	−0.004609	0.8413
rs1801282	PPARG_2	3	12393125	850	0.006047	0.8467
rs1611115	DBH_2	9	136500515	848	0.004472	0.8517
rs3745833	GALP	19	56693620	848	0.003907	0.8558
rs8191992	CHRM2_2	7	136701308	851	−0.002478	0.9022
rs2802	FOXO3A	19	58315273	849	0.002538	0.9058
rs324650	CHRM2_1	7	136693661	851	−0.001108	0.9556
rs1042713	ADRB2_1	5	148206440	843	0.0009467	0.9626
rs16147	NPY	7	24323410	850	0.000411	0.9832

Notes: None of the SNP associations in Supplemental Table 2 Bonferroni-corrected significance level of p = 0.00089. Significant results are in bold.

SUPPLEMENTAL TABLE 3. SNP × Age Interactions for Resilience

SNP	Gene	Chromosome	Base Pair	N	Beta	SNPxAge p
rs7209436	*CRHR1*	17	43870142	734	0.2152	**0.01116**
rs534654	*CLOCK*	4	56290220	740	0.2275	**0.03032**
rs12474609	*LRP1B*	2	141721142	741	−0.2259	**0.03863**
rs662	*PON1*	7	94937446	740	−0.176	0.05471
rs179973	*CCKAR*	6	16362388	741	−0.1914	0.06429
rs6871510	*HOMER1*	5	78792344	741	−0.1867	0.06541
rs3745833	*GALP*	19	56693620	738	0.1671	0.06811
rs242940	*CRHR1*	17	43892600	738	0.1475	0.07799
rs1800908	*CCKAR*	4	26492222	741	−0.5175	0.08033
rs1799990	*PRNP*	20	4680251	729	0.1397	0.118
rs6314	PPP1R1B	13	47409034	730	0.2343	0.1252
rs2227956	Hsp70	6	31778272	737	0.1603	0.1394
rs1800497	DRD2/ANKK1	11	113270828	739	−0.1588	0.1516
rs8191992	CHRM2	7	136701308	741	−0.1126	0.188
rs1801133	MTHFR	1	11856378	739	−0.1187	0.1923
rs1800792	FGG	4	155534408	739	−0.1058	0.1975
rs6280	DRD3	3	113890815	739	−0.1141	0.2164
rs1801282	PPARG	3	12393125	740	−0.1666	0.2391
rs1205	CRP	1	159682233	740	0.1075	0.2432
rs9664222	MINPP1	10	89338633	735	−0.1139	0.2736
rs162431	PYY	17	42030175	726	−0.1867	0.2965
rs1360780	FKBP5	6	35607571	740	0.09115	0.3177
rs363039	SNAP25	20	10220496	730	−0.08773	0.3219
rs1800896	IL10	1	206946897	741	−0.0855	0.3402
rs2061174	CHRNA7	7	136661400	740	0.07515	0.4066
rs2070592	PYY	17	42031331	734	0.07642	0.4109
rs7412	ApoE4	19	45412079	710	−0.1132	0.4457
rs2760118	PON1	6	24503590	741	0.0672	0.4746
rs1611115	DBH	9	136500515	738	0.06369	0.5212
rs5882	CETP	16	57016092	739	0.05196	0.5286
rs2830102	APP	21	27535027	741	0.0466	0.6114
rs1042714	ADRB2	5	148206473	734	0.0417	0.6313
rs17070145	WWC1 (KIBRA)	5	167845791	741	−0.04069	0.6599
rs2802	FOXO3A	19	58315273	739	−0.0376	0.6762
rs1108580	DBH	9	136505114	730	0.03203	0.7072
rs3800324	PGBD1	6	28264681	739	0.0712	0.7353
rs4680	COMT	22	19951271	739	−0.02565	0.7683
rs1800629	TNF-alpha	6	31543031	725	0.03349	0.7812
rs11622883	GWA 14q32.13	14	95155776	738	0.02231	0.7971
rs7103411	BDNF	11	27700125	736	0.02048	0.8397
rs1800795	IL-6	7	22766645	738	−0.01663	0.8428
rs16147	NPY	7	24323410	740	−0.01488	0.8563
rs17571	CTSD	11	1782594	738	0.02297	0.8571
rs16944	IL1B	2	113594867	724	−0.01485	0.8819
rs10793294	GAB2	11	77996403	741	0.01529	0.8834
rs2725335	WRN	8	30892513	739	−0.02555	0.8876
rs821616	DISC1	1	232144598	741	0.01084	0.9037
rs1554948	TNK1	17	7286326	735	0.01012	0.9039
rs1131497	SORL1	11	121502745	741	−0.008959	0.9187
rs1042713	ADRB2	5	148206440	734	0.006168	0.9444
rs324650	CHRM2	7	136693661	741	−0.003885	0.9623
rs3758391	SIRT1	10	69643342	740	0.003241	0.9717
rs429358	ApoE4	19	45411941	703	−0.004076	0.9747
rs6265	BDNF	11	27679916	736	0.0001932	0.9986

Notes: None of the SNP associations in Supplemental Table 3 reached Bonferroni-corrected significance level of p = 0.00089. Significant results are in bold.

SUPPLEMENTAL TABLE 4. SNP × Maternal Education Interactions for Optimism

SNP	Gene	Chromosome	Base Pair	N	Beta	SNPxMatEdu p
rs7103411	BDNF	11	27700125	742	0.1239	**0.04398**
rs2227956	Hsp70	6	31778272	741	0.1285	0.05109
rs2070592	PYY	17	42031331	741	0.09754	0.07259
rs6265	BDNF	11	27679916	743	0.1063	0.1028
rs1801282	PPARG	3	12393125	746	−0.1271	0.1481
rs1360780	FKBP5	6	35607571	747	−0.08274	0.1638
rs1799990	PRNP	20	4680251	736	0.07717	0.1803
rs1611115	DBH	9	136500515	744	−0.08365	0.1968
rs242940	CRHR1	17	43892600	745	−0.05917	0.2319
rs10793294	GAB2	11	77996403	747	0.08005	0.2533
rs1042714	ADRB2	5	148206473	741	0.05915	0.2536
rs662	PON1	7	94937446	746	−0.06348	0.2653
rs1108580	DBH	9	136505114	738	−0.0584	0.3036
rs1800795	IL-6	7	22766645	745	0.05734	0.3111
rs4680	COMT	22	19951271	744	−0.04633	0.3763
rs8191992	CHRM2	7	136701308	747	0.04719	0.3844
rs2725335	WRN	8	30892513	745	0.09502	0.3871
rs6280	DRD3	3	113890815	746	−0.04814	0.4128
rs9664222	MINPP1	10	89338633	741	0.04983	0.4397
rs12474609	LRP1B	2	141721142	746	0.05425	0.4413
rs16147	NPY	7	24323410	747	0.0398	0.4536
rs1800497	DRD2/ANKK1	11	113270828	745	0.05025	0.4758
rs17070145	WWC1 (KIBRA)	5	167845791	747	−0.04045	0.4772
rs3758391	SIRT1	10	69643342	746	0.03961	0.4872
rs1800896	IL10	1	206946897	747	0.03747	0.503
rs162431	PYY	17	42030175	729	0.0656	0.5089
rs3800324	PGBD1	6	28264681	746	0.07761	0.5213
rs363039	SNAP25	20	10220496	735	−0.03668	0.5324
rs1131497	SORL1	11	121502745	747	0.03016	0.5597
rs2830102	APP	21	27535027	748	0.03142	0.5838
rs16944	IL1B	2	113594867	728	−0.03017	0.6406
rs2802	FOXO3A	19	58315273	745	0.02749	0.6499
rs1800908	CCKAR	4	26492222	748	−0.06769	0.6742
rs1042713	ADRB2	5	148206440	740	−0.02236	0.6816
rs1205	CRP	1	159682233	747	0.02332	0.6839
rs1800629	TNF-alpha	6	31543031	728	0.02893	0.6997
rs2061174	CHRNA7	7	136661400	748	0.01902	0.732
rs6871510	HOMER1	5	78792344	747	0.01864	0.7625
rs429358	ApoE4	19	45411941	710	−0.0224	0.7626
rs7209436	CRHR1	17	43870142	740	0.01414	0.7868
rs17571	CTSD	11	1782594	745	0.01952	0.7904
rs3745833	GALP	19	56693620	745	−0.01303	0.8161
rs1800792	FGG	4	155534408	745	0.01128	0.8307
rs2760118	PON1	6	24503590	747	0.01157	0.8336
rs1801133	MTHFR	1	11856378	744	0.01139	0.8354
rs1554948	TNK1	17	7286326	742	0.01094	0.8387
rs534654	CLOCK	4	56290220	746	0.01244	0.8436
rs11622883	GWA_14q32.13	14	95155776	746	0.009417	0.8592
rs179973	CCKAR	6	16362388	747	0.01192	0.8594
rs7412	ApoE4	19	45412079	718	0.01444	0.8771
rs5882	CETP	16	57016092	745	−0.006026	0.9113
rs821616	DISC1	1	232144598	747	−0.006258	0.9139
rs324650	CHRM2	7	136693661	747	0.005311	0.9194
rs6314	PPP1R1B	13	47409034	735	0.008687	0.9233

Notes: MatEdu: maternal education. None of the SNP associations in Supplemental Table 4 reached Bonferroni-corrected significance level of p = 0.00089. Significant results are in bold.

SUPPLEMENTAL TABLE 5. SNP × Maternal Education Interactions for Resilience

SNP	Gene	Chromosome	Base Pair	N	Beta	SNPxMatEdu p
rs242940	CRHR1	17	43892600	650	−0.5322	**0.006695**
rs7209436	CRHR1	17	43870142	644	−0.5392	**0.008364**
rs7412	ApoE4	19	45412079	625	0.8443	**0.02319**
rs12474609	LRP1B	2	141721142	651	0.6123	**0.02983**
rs9664222	MINPP	10	89338633	645	0.496	**0.03713**
rs2070592	PYY	17	42031331	645	0.3936	0.0731
rs662	PON1	7	94937446	650	−0.3874	0.0841
rs2760118	PON1	6	24503590	651	0.3695	0.09982
rs4680	COMT	22	19951271	649	−0.3166	0.1157
rs3745833	GALP	19	56693620	649	−0.2743	0.1998
rs16147	NPY	7	24323410	651	0.2701	0.2046
rs1800896	IL10	1	206946897	651	0.2613	0.2483
rs1205	CRP	1	159682233	650	0.2461	0.283
rs10793294	GAB2	11	77996403	651	−0.2945	0.2917
rs16944	IL1B	2	113594867	636	0.2642	0.294
rs5882	CETP	16	57016092	649	−0.2152	0.2965
rs3800324	PGBD1	6	28264681	650	0.5166	0.3079
rs6280	DRD3	3	113890815	650	0.2246	0.3184
rs1800629	TNF-alpha	6	31543031	636	−0.3041	0.3295
rs17070145	WWC1 (KIBRA)	5	167845791	651	−0.2207	0.3403
rs1360780	FKBP5	6	35607571	650	0.2072	0.359
rs1801133	MTHFR	1	11856378	649	−0.1893	0.3838
rs2227956	Hsp70	6	31778272	647	−0.2218	0.3869
rs2061174	CHRNA7	7	136661400	651	−0.1772	0.4133
rs17571	CTSD	11	1782594	649	0.2129	0.4752
rs2725335	WRN	8	30892513	649	0.3345	0.4756
rs324650	CHRM2	7	136693661	651	0.1487	0.4766
rs8191992	CHRM2	7	136701308	651	0.137	0.5168
rs7103411	BDNF	11	27700125	647	0.1647	0.52
rs11622883	GWA_14q32.13	14	95155776	651	−0.1171	0.5728
rs162431	PYY	17	42030175	637	−0.2227	0.5833
rs179973	CCKAR	6	16362388	651	0.1476	0.5844
rs1800908	CCKAR	4	26492222	652	0.334	0.6002
rs429358	ApoE4	19	45411941	620	0.1539	0.6004
rs363039	SNAP25	20	10220496	640	−0.1097	0.6317
rs534654	CLOCK	4	56290220	650	−0.119	0.6331
rs1799990	PRNP	20	4680251	640	0.1069	0.6413
rs6871510	HOMER1	5	78792344	651	0.1073	0.6752
rs2830102	APP	21	27535027	652	−0.09353	0.6824
rs1042713	ADRB2	5	148206440	645	0.07666	0.7259
rs1800792	FGG	4	155534408	649	0.05224	0.7924
rs1131497	SORL1	11	121502745	651	−0.05238	0.8038
rs821616	DISC1	1	232144598	651	0.05419	0.8186
rs3758391	SIRT1	10	69643342	650	−0.04532	0.8445
rs1611115	DBH	9	136500515	648	0.0496	0.8497
rs1108580	DBH	9	136505114	641	0.02978	0.897
rs1801282	PPARG	3	12393125	650	−0.03035	0.9328
rs1554948	TNK1	17	7286326	646	0.01839	0.9329
rs1800497	DRD2/ANKK1	11	113270828	650	−0.01343	0.9633
rs1042714	ADRB2	5	148206473	646	0.005564	0.9785
rs6314	PPP1R1B	13	47409034	641	0.009812	0.9785
rs2802	FOXO3A	19	58315273	649	−0.005068	0.9829
rs6265	BDNF	11	27679916	647	0.002197	0.9937
rs1800795	IL-6	7	22766645	649	−0.001362	0.9953

Notes: MatEdu: maternal education. None of the SNP associations in Supplemental Table 5 reached Bonferroni-corrected significance level of p = 0.00089. Significant results are in bold.