

Longevity Candidate Genes and Their Association With Personality Traits in the Elderly

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Human longevity and personality traits are both heritable and are consistently linked at the phenotypic level. We test the hypothesis that candidate genes influencing longevity in lower organisms are associated with variance in the five major dimensions of human personality (measured by the NEO-FFI and IPIP inventories) plus related mood states of anxiety and depression. Seventy single nucleotide polymorphisms (SNPs) in six brain expressed, longevity candidate genes (*AFG3L2*, *FRAP1*, *MAT1A*, *MAT2A*, *SYNJ1*, and *SYNJ2*) were typed in over 1,000 70-year old participants from the Lothian Birth Cohort of 1936 (LBC1936). No SNPs were associated with the personality and psychological distress traits at a Bonferroni corrected level of significance ($P < 0.0002$), but there was an over-representation of nominally significant ($P < 0.05$) SNPs in the *synaptotagmin-2* (*SYNJ2*) gene associated with agreeableness and symptoms of depression. Eight SNPs which showed nominally significant association across personality measurement instruments were tested in an extremely large replication sample of 17,106 participants. SNP rs350292, in *SYNJ2*, was significant: the minor allele was associated with an average decrease in NEO agreeableness scale scores of 0.25 points, and 0.67 points in the restricted analysis of elderly cohorts (most aged > 60 years). Because we selected a specific set of longevity genes based on functional genomics findings, further research on other longevity gene candidates is warranted to discover whether they are relevant candidates for personality and psychological distress traits. © 2011 Wiley Periodicals, Inc.

Key words: NEO personality; IPIP personality; anxiety; depressive symptoms; aging; genetics

INTRODUCTION

Individual differences in personality traits are influenced by genetic variation, and these genetic effects mostly endure across the lifespan [Viken et al., 1994; Bratko and Butkovic, 2007; Blonigen et al., 2008]. Specific personality traits (e.g., high conscientiousness and low neuroticism) are predictive of longevity (which itself shows familial influence) [Terracciano et al., 2008], so it follows that candidate genes for longevity might be associated with various personality dimensions. There is likely no single mechanism to explain the link between personality traits and longevity. It might be that physiological changes in old age result in personality changes (e.g., worsening physical health leads someone to be more depressed) or that certain personality types engage in behaviors conducive to survival. But if either of the causal traits shows genetic variability that influences intermediary behaviors then this should also be detected in the correlated trait. Alternately, there may be a genetic correlation between personality and longevity resulting from genetic pleiotropy, for instance, a gene that influences the stress response could have effects on personality and longevity. In this study, we test the association of six longevity candidate genes—that were identified through a comparative functional genomics study [Smith et al., 2008]—with measures of personality and related measures of anxiety and depression in an elderly cohort and in replication cohorts.

The five major dimensions of personality include neuroticism (characterized by e.g., emotional sensitivity, and a tendency toward

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anxiety), extraversion (e.g., outgoingness, sociability), openness to experience (e.g., interest in intellectual pursuits, arts, ideas), conscientiousness (e.g., dutifulness, organization), and agreeableness (e.g., non-confrontational, easy to get along with) [Costa and McCrae, 1992]. Each has been studied in relation to longevity (in both normally aging and exceptionally long-lived samples), with conscientiousness being the most consistently associated personality trait. A meta-analysis of 20 studies confirmed a significant positive correlation ($r = .11$, 95% confidence interval of 0.05–0.17) between conscientiousness and longevity [Kern and Friedman, 2008]. With regard to the other traits, a study of 246 offspring (mean age of 75 years) of centenarians showed that they were more extraverted and less neurotic, and women more agreeable than the normative mean population levels [Givens et al., 2009]. This agreed with findings from the Baltimore Longitudinal Study of Aging: among deceased participants, those scoring above 1 standard deviation from the mean on the general activity facet of extraversion, emotional stability, or conscientiousness had lived 2–3 years longer than those in the reversed tail of the distributions [Terracciano et al., 2008]. In Weiss and Costa's [2005] analysis of the NEO-PI-R, agreeableness and conscientiousness (and a trend for neuroticism) were protective for survival over 3 years in 66- to 102-year olds. Such personality–longevity associations might even be stronger if gene by environment interaction effects are present.

Animal studies confirm a role of genes in longevity [Brown-Borg, 2007; Kuningas et al., 2008], which complements human twin studies of deaths from age-related disease, and family studies of centenarians that show genetic effects explaining between one quarter to half of the variability in longevity [Herskind et al., 1996; Christensen et al., 2006; Melzer et al., 2007]. The identification of genes involved in age-related diseases has focused predominantly on pathways involved in cell cycle control, oxidative stress, insulin, other endocrine signaling, and inflammation [Cluett and Melzer, 2009]. In comparative functional genomics, Smith et al. [2008] was the first to assess the extent to which longevity genes are conserved between highly divergent eukaryotic species by comparing the yeast *Saccharomyces cerevisiae* and the nematode

Caenorhabditis elegans. They identified 25 aging genes in *C. elegans* that were conserved in their yeast relatives and were therefore good candidate genes for aging in humans. We selected a subset of these candidate genes comprising all those that are brain-expressed and evolutionary-conserved—*AFG3L2*, *FRAP1*, *MAT1A*, *MAT2A*, *SYNJ1*, and *SYNJ2*—which we hypothesized would be relevant for personality and mood traits in an aging cohort. The first gene found to alter aging—located in the insulin-like signaling pathway—was discovered in *C. elegans* and subsequent studies suggest that innate immunity is influenced by this pathway and that it is conserved from yeast to humans [Amrit and May, 2010]. There are known associations between inflammatory biomarkers and personality in humans [Sutin et al., 2010], illustrative of potential mechanisms which might underlie personality–longevity associations, that is, through pleiotropic effects acting on the immune and central nervous systems. The recently discovered set of conserved genes in *C. elegans* might also uncover biological pathways of relevance to individual differences in human aging and their associations with personality differences.

We test a specific set of candidate longevity genes—identified by comparative functional genomics—in humans in relation to non-cognitive psychological traits and states. Haplotype-tagging single nucleotide polymorphisms (SNPs) in each of these genes were genotyped in an elderly Scottish cohort (mean age of 70 years) and tested for their association with measures of personality and psychological distress, which are predictive of longevity. Associations were followed up in independent replication cohorts, including elderly samples from Finland, Italy, USA, and Germany.

MATERIALS AND METHODS

Subjects—LBC1936

All participants were born in 1936 and had taken part in the Scottish Mental Survey of 1947; they were tested on psychological (including mood) and medical traits at about 70 years of age at the Wellcome Trust Clinical Research Facility (WTCRF: Western General Hospital, Edinburgh) and completed some questionnaires (including personality) at home [Deary et al., 2007]. The sample was Caucasian and lived independently in the Lothian region (Edinburgh city and surrounding area) of Scotland. Further description about participant recruitment can be found elsewhere [Deary et al., 2007]. DNA samples and psychological distress data were available for 1,078 participants. The available personality data gave an analysis sample of $N = 951$ for these traits of 470 men and 481 women. The mean age of the sample was 69.5 years ($SD = 0.8$). The mood states of anxiety and depression were assessed using the Hospital Anxiety Depression Scale (HADS) [Zigmond and Snaith, 1983]. The personality traits of the Five Factor model (Introduction Section) were measured using the NEO Five-Factor Inventory [NEO-FFI; Costa and McCrae, 1992]. The NEO-FFI is a 60-item inventory consisting of 12 items for each of the five factors. Participants also completed the IPIP Big-Five 50-item inventory [Goldberg, 1999], consisting of 10 items for each of the Big-Five personality factors. The participants were given the personality questionnaires with written instructions at the end of their clinic visit and asked to return them by post.

SNP Selection

SNPs with a minor allele frequency (MAF) greater than 0.05 were selected using Tagger [de Bakker et al., 2005] in Haploview v 4.1 [Barrett et al., 2005] based on the Hapmap CEPH population (Release 22) data. Using pairwise tagging ($r^2 = .80$), 70 SNPs tagged haplotypes from the specific gene regions and 5 kb either side of the gene, although 1 of these SNPs was excluded due to high-linkage disequilibrium with another tagged SNP. They served as direct proxies to all other untyped SNPs in the six genes because they are highly correlated with one another. Non-synonymous SNPs were also included as haplotype-tagging SNPs. The UCSC genome browser [Karolchik et al., 2008] was used to identify non-synonymous SNPs—rs2502601 in exon 27 of *SYNJ2* a missense substitution (G = Gly, A = Glu, Glu1468Gly) and rs2254562 in exon 8 of *SYNJ1* a missense substitution (G = Arg, A = Lys, Lys295Arg), giving 70 SNPs in total.

Genotyping

Genomic DNA was isolated from whole blood by standard procedure at the WTCRF Genetics Core, Western General Hospital, Edinburgh. Forty-nine SNPs were genotyped using a competitive allele-specific PCR system (KASPar) by Kbiosciences, Herts, UK. A further 21 SNPs—all in *SYNJ2*—were genotyped using the Illumina Human610-Quadv1 Chip (for more detail see Luciano et al. [2011]).

Genotype Data

The mean genotyping rate was 99% (range: 92–100%) and MAF were >0.04 (see Online Resource Table I for marker position and MAFs). Genotype frequencies were similar to the HapMap CEPH population (mean difference in genotype frequencies = 0.03, minimum 0.002, maximum 0.08), and all SNPs were in Hardy–Weinberg equilibrium (HWE) as judged by the HWE exact SNP tests (all P -values >0.001) in Haploview.

Statistical Analysis and Power

Association tests were performed for individual SNPs in PLINK [Purcell et al., 2007] using the regression option (additive model) and including sex and age as covariates. The statistical power to detect a genetic effect size of 1% (for MAF of 0.25) was 90.8% [Purcell et al., 2003]. Because a large number of measures and SNPs were investigated, a Bonferroni correction was applied that resulted in a new significance criterion of 0.0002. This was based on correcting for five independent factors; that is, the five major personality dimensions (anxiety and depression are aligned with the neuroticism factor) multiplied by the number of independent SNPs. Nyholt's [2004] SNP Spectral Decomposition program was used to estimate SNP independence within genes, resulting in a correction for 46 independent SNPs.

Replication Cohorts

Personality traits. Eleven cohorts were available in which to replicate any associations for NEO personality measures. These

cohorts were of European descent and are described by de Moor et al. [in press]. In brief, they comprised samples of varying age range (15–87 years) from Italy (Cilento, Sardinia), The Netherlands (NTR/NESDA, ERF), United States (BLSA, SAGE), Finland (HBCS), Australia (QIMR, NAG/IRPG), Estonia (EGPUT), and Germany, totaling 17,106 participants with mean age ranging from 19.4 ± 3 (Australia: QIMR) to 78.9 ± 5.4 (Italy: Cilento) years. Personality scores for the five factors were based on the 60 items of the NEO-FFI (12 items per factor) [Costa and McCrae, 1992]. SNP data were available from varying sized genome-wide scans which had all been imputed to ~ 2.4 M SNPs using HAPMAP II data. Association analysis of each SNP (under an additive model) had been performed using either PLINK, SNPTEST, or MERLIN [de Moor et al., in press]. The results for selected longevity candidate gene SNPs were meta-analyzed using METAL [Willer et al., 2010]. Two separate meta-analyses of older cohorts (HBCS, BLSA, Cilento, Germany: mean age >63.4 years; $N = 2,555$) and younger cohorts (Sardinia, NTR/NESDA, ERF, SAGE, NAG/IRPG, QIMR, EGPUT: mean age <49.3 years; $N = 14,551$), then a combined analysis, were performed.

Anxiety and Depression Traits

HADS data were available in an independent cohort of 517 participants from the Lothian region, born in 1921 (LBC1921) and assessed on psychological distress at ~ 79 years [Deary et al., 2004]. Further details of the mood inventory data collection can be found by Gow et al. [2005]. SNP genotyping was performed with the Illumina Human610-Quadv1 Chip with SNPs imputed to ~ 2.4 M based on HAPMAP II data (for further details see Luciano et al. [2011]). Replication testing, using PLINK, was performed for association findings from the main analysis.

RESULTS

The anxiety and depression scores from the HADS were negatively skewed and were square-root transformed to improve their distribution. All personality measures showed distributions close to normality. Descriptive statistics for the NEO-FFI, IPIP, and HADS measures appear in Table I. Consistent with prior evidence, sex differences (women scoring higher) were observed for HADS anxiety ($P < .001$), NEO and IPIP neuroticism ($P < .01$), and agreeableness ($P < .0001$). NEO openness to experience ($P < .0001$) and extraversion ($P < .05$) scores were also higher in women but their corresponding IPIP factors showed no sex differences. Age effects were observed for NEO and IPIP conscientiousness ($P < .05$), such that lower scores tended to be associated with older age. However, the age range in the sample is very small.

The results of the association tests for personality and psychological distress measures in the LBC1936 are shown in the Online Resource Table I, these will be described. No SNPs surpassed the Bonferroni corrected significance level for any of the traits. However, for agreeableness, there were a larger number of nominally significant findings ($P < .05$) than for the other measures: 10 for the IPIP and 6 for the NEO. For IPIP agreeableness all of the nominally significant SNPs were located in the *SYNJ2* gene (in independent SNPs), more than would be expected by chance (with 0.05 probability) assuming 44 tests. For NEO agreeableness, an additional SNP (rs2254562) was observed in the *SYNJ1* gene. The most significant SNP for agreeableness, located in *SYNJ2*, was rs12202135 ($P = 0.0003$ for IPIP; $P = 0.01$ for NEO); MAF of this SNP was 0.13. Ten SNPs were nominally significant for depression, with all of these located in *SYNJ2* (more than expected by chance); the most significant SNP was rs10046389 ($P = 0.004$) with a MAF of 0.40. Another of these SNPs (rs1750043) was also associated with anxiety ($P = 0.01$; MAF: 0.48). High conscientiousness and low neuroticism have been especially linked with longevity, but the association

TABLE I. Sample Size, Range, Mean, and Standard Deviation of Personality and Psychological Distress Scales in the LBC1936

	N	All Range; Mean [SD]	Men Range; Mean [SD]	Women Range; Mean [SD]
IPIP				
Emotional stability	950	1–40; 24.6 [7.7]	1–40; 25.5 [7.6]	1–40; 23.7 [7.6]
Extraversion	954	0–40; 21.3 [7.1]	0–40; 21.0 [7.3]	0–40; 21.6 [6.8]
Intellect	948	5–40; 23.8 [5.7]	5–40; 23.8 [5.8]	5–40; 23.9 [5.6]
Agreeableness	952	5–40; 31.1 [5.4]	5–40; 29.0 [5.4]	14–40; 23.1 [4.6]
Conscientiousness	952	9–40; 28.2 [6.0]	10–40; 28.0 [5.9]	9–40; 28.5 [6.1]
NEO-FFI				
Neuroticism	954	0–47; 17.1 [7.6]	0–41; 15.7 [7.6]	1–47; 18.4 [7.4]
Extraversion	943	6–43; 27.0 [5.9]	9–42; 26.6 [6.1]	6–43; 27.4 [5.8]
Openness	947	9–43; 26.0 [5.8]	9–42; 25.2 [5.7]	12–43; 26.9 [5.8]
Agreeableness	954	17–47; 33.5 [5.3]	17–47; 31.8 [5.2]	22–47; 35.0 [4.8]
Conscientiousness	947	11–48; 34.7 [6.0]	11–48; 34.4 [6.0]	14–48; 34.9 [5.9]
Psychological distress				
HADS anxiety	1,089	0–17; 4.9 [3.2]	0–16; 4.2 [2.9]	0–17; 5.6 [3.3]
HADS depression	1,086	0–16; 2.8 [2.2]	0–16; 2.9 [2.3]	0–11; 2.7 [2.1]

results were predominantly null for conscientiousness (3 SNPs nominally associated with NEO and 1 non-overlapping SNP with IPIP). Eight SNPs were associated with IPIP emotional stability, 2 of which (rs10455936, MAF, 0.22; rs9459093, MAF, 0.43) located in *SYNJ2* overlapped with significant SNPs for NEO neuroticism. Because a large number of SNPs (i.e., 44) was typed in *SYNJ2* the linkage disequilibrium between them is shown in Figure 1; note that 24 independent SNPs were derived by SNP Spectral Decomposition.

Across all traits, standardized coefficients for nominally significant associations ranged between 0.06 and 0.11. A reduced set of SNPs which were nominally associated with both NEO and IPIP scales or with both psychological distress and emotional stability (and therefore deemed more reliable associations) in the LBC1936 are shown in Table II. Replication of these SNPs was sought in independent cohorts. Table III shows the replication results for the personality traits. One of these SNPs, rs350292 (located in intron 18 of *SYNJ2*; MAF: 0.11), was significantly associated with agreeableness in the older cohorts ($P = 0.0059$), and at a reduced level in the combined older and younger cohorts meta-analysis. Within the 11 individual cohorts tested, nominal significance was observed in 3 of these (ERF, $P = 0.049$; HBCS, $P = 0.038$; BSA, $P = 0.048$), with two being aging cohorts where the mean ages were 63.4 ± 3 years (HBCS) and 68.5 ± 17 years (BSA). The allele effects in these cohorts were in the same direction as the original association in LBC1936: the unstandardized regression coefficient was -0.67 in

the older cohort replication meta-analysis versus -0.93 in the LBC1936 cohort (the A allele relating to lower agreeableness scores). For psychological distress measures there were no significant associations in the LBC1921 cohort, $P > 0.18$.

DISCUSSION

A priori evidence of an association between personality and longevity [Terracciano et al., 2008] led us to test the association between a specific set of longevity candidate genes—established via a functional genomics study—and personality, anxiety, and depression measures. Of the six genes tested, *SYNJ2* showed a heightened number of SNPs that were nominally significant at an uncorrected level for measures of agreeableness and depression, and to a lesser extent, neuroticism.

Due to their increased association with longevity, conscientiousness and neuroticism were especially hypothesized to associate with longevity candidate genes, but neither of these traits showed strong evidence of association with any of the genes. Most notable were the SNPs in *SYNJ2* that showed P -values lower than 0.05 for NEO neuroticism (5 SNPs) and IPIP emotional stability (6 SNPs). SNPs in this same gene were also associated with agreeableness and depression scores, although they too did not exceed the corrected probability threshold. There is biological evidence to suggest *SYNJ2* may have a plausible role in disordered mood. Decreased expression of *SYNJ2* has been shown in the temporal cortex of major depressive

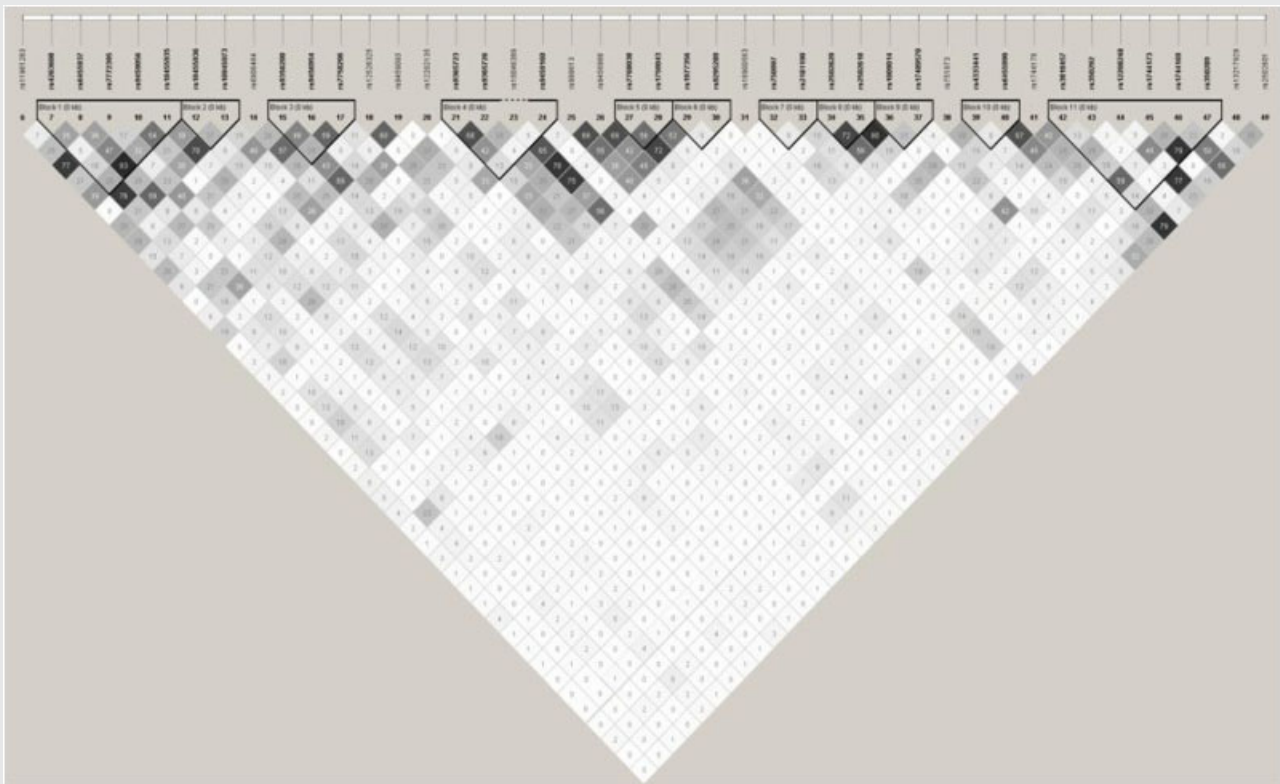


FIG. 1. The linkage disequilibrium structure (including r^2) for the region genotyped in *SYNJ2* in the LBC1936.

TABLE II. Effect Size (Standardized Regression Coefficient) and Significance of Haplotype-Tagging Longevity Gene SNPs That Are Nominally Significant for At Least Two Correlated Traits (i.e., the Same NEO and IPIP Scale or Psychological Distress and Neuroticism Measures) in the LBC1936.

Gene	Anxiety		Depression		NEO N		IPIP ES		NEO E		IPIP E		NEO O		IPIP I		NEO A		IPIP A		NEO C		IPIP C	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
<i>MAT2A</i>																								
rs14446669	-0.01	0.85	0.00	1	-0.01	0.80	0.02	0.65	-0.03	0.43	-0.03	0.32	-0.07	0.04	-0.06	0.05	-0.01	0.87	-0.05	0.10	-0.03	0.34	-0.02	0.52
<i>SYNJ2</i>																								
rs4263608 ^a	0.05	0.12	0.07	0.03	0.07	0.04	-0.06	0.09	-0.06	0.10	-0.05	0.13	0.00	0.92	-0.03	0.31	-0.01	0.79	-0.02	0.51	-0.05	0.13	-0.05	0.16
rs6455937 ^b	0.07	0.03	0.02	0.49	0.04	0.25	- 0.07	0.04	-0.01	0.83	- 0.07	0.05	-0.03	0.43	-0.04	0.22	0.04	0.25	0.04	0.20	0.00	0.99	-0.02	0.65
rs10455935 ^b	0.07	0.02	0.00	0.91	0.05	0.12	- 0.08	0.02	0.01	0.89	- 0.07	0.03	-0.03	0.32	-0.04	0.20	0.02	0.53	0.06	0.07	0.01	0.76	0.00	0.95
rs10455936 ^a	0.06	0.07	0.05	0.09	0.07	0.03	- 0.07	0.04	-0.05	0.12	- 0.07	0.03	-0.01	0.75	-0.05	0.16	-0.01	0.72	-0.01	0.79	-0.02	0.51	-0.02	0.47
rs10945973	0.08	0.01	-0.01	0.75	-0.06	0.08	0.07	0.03	-0.02	0.50	0.06	0.06	0.03	0.42	0.03	0.30	-0.03	0.33	-0.03	0.34	-0.01	0.77	0.00	0.94
rs12202135	0.02	0.53	- 0.07	0.03	-0.02	0.64	0.02	0.54	0.02	0.66	0.01	0.74	0.01	0.67	-0.03	0.39	0.09	0.01	0.11	0.00*	0.05	0.15	0.04	0.29
rs9459093	0.05	0.08	0.04	0.18	0.07	0.03	- 0.10	0.00*	-0.02	0.61	-0.04	0.21	-0.03	0.29	-0.06	0.08	0.02	0.64	0.01	0.80	-0.04	0.27	0.03	0.39
rs9459160	0.04	0.17	-0.03	0.35	0.02	0.46	0.01	0.70	0.05	0.17	0.04	0.18	0.03	0.35	-0.04	0.20	0.07	0.03	0.08	0.01	0.02	0.52	-0.02	0.65
rs1750043	0.08	0.01	0.06	0.04	0.03	0.38	-0.04	0.23	-0.03	0.36	-0.06	0.11	0.01	0.80	-0.04	0.30	-0.05	0.10	- 0.07	0.02	-0.04	0.29	-0.05	0.14
rs9295289	0.05	0.12	0.06	0.05	0.04	0.21	- 0.07	0.04	-0.01	0.85	-0.05	0.13	0.00	0.93	0.01	0.83	-0.05	0.16	-0.03	0.37	-0.01	0.74	0.00	0.97
rs350292	-0.03	0.35	0.03	0.37	-0.01	0.72	-0.01	0.76	0.01	0.85	0.03	0.33	0.00	0.91	0.00	0.90	- 0.08	0.01	- 0.07	0.03	-0.02	0.59	-0.03	0.43
rs1744173 ^c	0.03	0.36	-0.03	0.42	0.08	0.02	-0.03	0.41	- 0.09	0.01	- 0.09	0.01	0.01	0.68	-0.06	0.09	-0.03	0.31	-0.05	0.11	- 0.07	0.04	-0.03	0.46
rs350289 ^c	0.04	0.18	0.00	0.89	0.09	0.01	-0.05	0.16	- 0.09	0.01	- 0.09	0.01	0.02	0.52	-0.04	0.26	-0.04	0.17	- 0.07	0.03	- 0.07	0.03	-0.02	0.50

Values in bold are $P < 0.05$.

N, neuroticism; ES, emotional stability (reverse pole of N); E, extraversion; I, intellect; O, openness; A, agreeableness; C, conscientiousness.

^aLinkage disequilibrium (LD) $r^2 = 0.76$.

^bLD $r^2 = 0.83$.

^cLD $r^2 = 0.79$.

* $P < 0.005$.

TABLE III. Replication P-Values and Unstandardized Betas in the NEO Consortium of SNPs in *MAT2A* and *SYNJ2* That Were Identified in the LBC1936 as Nominally Associated With Measures of Both NEO and IPIP Personality

Measure	Gene SNP	Older cohorts		Younger cohorts		Combined	
		Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Openness	<i>MAT2A</i> rs1446669	0.00 [0.19]	0.98	0.03 [0.11]	0.80	0.05 [0.08]	0.56
Neuroticism	<i>SYNJ2</i> rs10455936	−0.08 [0.27]	0.76	−0.09 [0.15]	0.54	−0.13 [0.12]	0.26
Agreeableness	rs12202135	−0.02 [0.23]	0.92	0.07 [0.14]	0.64	0.02 [0.11]	0.83
Neuroticism	rs9459093	0.01 [0.21]	0.96	−0.02 [0.13]	0.86	0.01 [0.10]	0.91
Agreeableness	rs9459160	−0.26 [0.28]	0.36	0.15 [0.14]	0.31	0.10 [0.11]	0.37
Agreeableness	rs350292	−0.67 [0.25]	0.01*	−0.17 [0.14]	0.22	−0.25 [0.11]^a	0.02
Extraversion	rs1744173	0.25 [0.23]	0.27	−0.08 [0.15]	0.60	0.00 [0.11]	0.96
Extraversion	rs350289	0.11 [0.25]	0.66	−0.13 [0.16]	0.42	−0.07 [0.12]	0.58

P-values <0.05 are given in bold.

*P-value = 0.0059.

^a8 of 11 Cohorts showed beta effect in the same direction; note that the unstandardized beta estimate in LBC1936 was −0.93 with a standard error of 0.36.

disorder patients [Aston et al., 2005] and in a rodent model of depression overlap between cingulate cortex gene expression, stress behavior, and anti-depressant response identified *SYNJ2* as a candidate gene for therapeutic targets [Surget et al., 2009]. While this is aligned with our findings of association with depression and neuroticism, our strongest support for *SYNJ2* was with agreeableness, where rs350292 showed association in our replication sample of more than 17,000 participants and the direction of the effect was consistent between the original and replication sample. Of note, the meta-analysis of older cohorts—but not the younger cohorts—showed a significant effect of this SNP with agreeableness. Agreeableness, particularly its straightforwardness facet, is predictive of survival in Americans older than 66 years [Weiss and Costa, 2005]. Six other SNPs in *SYNJ2* were in high-linkage disequilibrium with this SNP, but, like rs350292, they were all intronic SNPs, with no documented previous associations. Ours is the first association study to investigate *SYNJ2* and personality traits. Synaptojanins are a family of phosphoinositide phosphatases; and like synaptojanin 1, mammalian synaptojanin 2 is involved in dynamin and clathrin-mediated synaptic vesicle recycling, but distinct from *SYNJ1*, it is expressed more widely (both are concentrated in nerve terminals), and is linked to membrane trafficking and signal transduction pathways [Nemoto et al., 1997; Nemoto et al., 2001].

The only gene that has been tested previously for association with traits relevant to our study was the *SYNJ1* gene. It is a phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P₂) involved in clathrin-coated pit dynamics, which are required for efficient synaptic vesicle endocytosis and re-availability at nerve terminals [Perera et al., 2006]. It was identified in a linkage region for bipolar disorder, but the association analysis results of this gene with depression have been inconsistent. Stopkova et al. [2004] did not find differences in allele frequencies between controls and bipolar patients for a common mutation, and previous rare variants in this gene were not detected in their sample. However, one of the homozygote groups was overrepresented among bipolar patients in one of their

samples. In our study, no SNPs in *SYNJ1* were associated with depression or associated measures of anxiety and neuroticism, suggesting that the effects of this gene on depression may be limited to rare mutations if they are important at all.

Our SNPs were chosen using information from HapMap, but one study which re-sequenced longevity candidates (including *FRAP1*) in healthy old adults showed that only 19% of variants in their sequencing set were observed in HapMap [Halaschek-Wiener et al., 2009]. It is possible, then, that we are missing important uncommon variants that do have effects on the longevity-related traits of personality and psychological distress. While it is possible that other genes or other factors may influence the relationship between personality and longevity, we can fairly confidently rule out common variants in the *AFG3L2*, *FRAP1*, *MAT1A*, *MAT2A*, and *SYNJ1* genes. Follow-up of further variants in *SYNJ2*, and especially in older cohorts, is needed before we can dismiss it as a candidate gene for personality and psychological distress in old-age. Genome-wide association studies both of longevity and personality [Newman et al., 2010; de Moor et al., in press] will serve as important repositories of gene associations that can be interrogated systematically for longevity candidate genes, such as *SYNJ2*. Furthermore, strategies focused on rare variants in longevity candidate genes could prove a fruitful approach.

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