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IMMEDIATE COMMUNICATION

Mood, stress and longevity: convergence on *ANK3*

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Antidepressants have been shown to improve longevity in *C. elegans*. It is plausible that orthologs of genes involved in mood regulation and stress response are involved in such an effect. We sought to understand the underlying biology. First, we analyzed the transcriptome from worms treated with the antidepressant mianserin, previously identified in a large-scale unbiased drug screen as promoting increased lifespan in worms. We identified the most robust treatment-related changes in gene expression, and identified the corresponding human orthologs. Our analysis uncovered a series of genes and biological pathways that may be at the interface between antidepressant effects and longevity, notably pathways involved in drug metabolism/degradation (nicotine and melatonin). Second, we examined which of these genes overlap with genes which may be involved in depressive symptoms in an aging non-psychiatric human population ($n = 3577$), discovered using a genome-wide association study (GWAS) approach in a design with extremes of distribution of phenotype. Third, we used a convergent functional genomics (CFG) approach to prioritize these genes for relevance to mood disorders and stress. The top gene identified was *ANK3*. To validate our findings, we conducted genetic and gene-expression studies, in *C. elegans* and in humans. We studied *C. elegans* inactivating mutants for *ANK3*/*unc-44*, and show that they survive longer than wild-type, particularly in older worms, independently of mianserin treatment. We also show that some *ANK3*/*unc-44* expression is necessary for the effects of mianserin on prolonging lifespan and survival in the face of oxidative stress, particularly in younger worms. Wild-type *ANK3*/*unc-44* increases in expression with age in *C. elegans*, and is maintained at lower youthful levels by mianserin treatment. These lower levels may be optimal in terms of longevity, offering a favorable balance between sufficient oxidative stress resistance in younger worms and survival effects in older worms. Thus, *ANK3*/*unc-44* may represent an example of antagonistic pleiotropy, in which low-expression level in young animals are beneficial, but the age-associated increase becomes detrimental. Inactivating mutations in *ANK3*/*unc-44* reverse this effect and cause detrimental effects in young animals (sensitivity to oxidative stress) and beneficial effect in old animals (increased survival). In humans, we studied if the most significant single nucleotide polymorphism (SNP) for depressive symptoms in *ANK3* from our GWAS has a relationship to lifespan, and show a trend towards longer lifespan in individuals with the risk allele for depressive symptoms in men (odds ratio (OR) 1.41, $P = 0.031$) but not in women (OR 1.08, $P = 0.33$). We also examined whether *ANK3*, by itself or in a panel with other top CFG-prioritized genes, acts as a blood gene-expression biomarker for biological age, in two independent cohorts, one of live psychiatric patients ($n = 737$), and one of suicide completers from the coroner's office ($n = 45$). We show significantly lower levels of *ANK3* expression in chronologically younger individuals than in middle age individuals, with a diminution of that effect in suicide completers, who presumably have been exposed to more severe and acute negative mood and stress. Of note, *ANK3* was previously reported to be overexpressed in fibroblasts from patients with Hutchinson–Gilford progeria syndrome, a form of accelerated aging. Taken together, these studies uncover *ANK3* and other genes in our dataset as biological links between mood, stress and longevity/aging, that may be biomarkers as well as targets for preventive or therapeutic interventions. Drug repurposing bioinformatics analyses identified the relatively innocuous omega-3 fatty acid DHA (docosahexaenoic acid), piracetam, quercetin, vitamin D and resveratrol as potential longevity promoting compounds, along with a series of existing drugs, such as estrogen-like compounds, antidiabetics and sirolimus/rapamycin. Intriguingly, some of our top candidate genes for mood and stress-modulated longevity were changed in expression in opposite direction in previous studies in the Alzheimer disease. Additionally, a whole series of others were changed in expression in opposite direction in our previous studies on suicide, suggesting the possibility of a "life switch" actively controlled by mood and stress.

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INTRODUCTION

> Age is an issue of mind over matter. If you don't mind, it doesn't matter.
>
> —Mark Twain

The merits of longevity and the perils of aging are the subject of active debate at a societal level, and of concerted scientific research. Longevity and aging may be influenced by, and in turn influence, both positive and negative mood and response to stress, due to teleological evolutionary reasons or mundane lifestyle consequences. On the negative side, individuals with mood disorders[1] and stress disorders[2] have a significantly shorter life expectancy. Aging can lead to depression, attributable at least in part to physical health problems and related disability.[3] This bidirectional relationship may have a genetic basis, and be susceptible to therapeutic interventions. We sought

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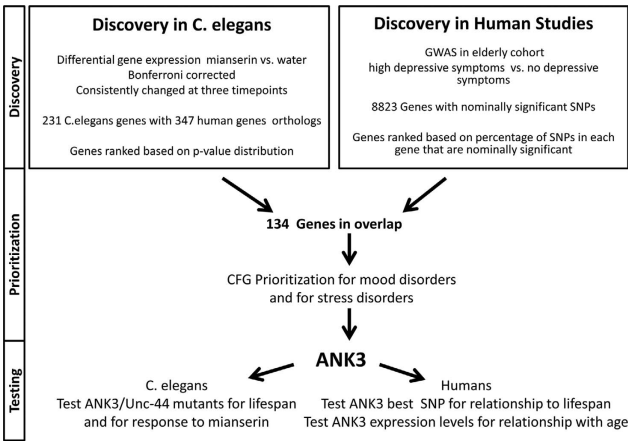


Figure 1. Flowchart of studies. Integration of *C. elegans* and human data for discovery, prioritization and testing. CFG, convergent functional genomics.

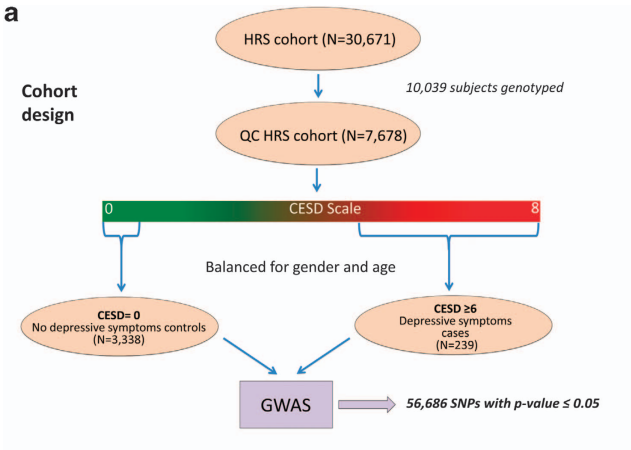
to understand the mediating genes by conducting a series of translational studies and analyses (Figure 1).

The atypical antidepressant mianserin, which treats depression and stress disorders,[4,5] was first identified as a longevity promoting compound in a large-scale screen for compounds that extend *C. elegans* lifespan.[6] More recently, we have shown that it increases longevity in *C. elegans* by preventing transcriptional drift.[7] We first analyzed the human orthologs of genes that were significantly and consistently changed in expression by mianserin treatment in *C. elegans*, and identified biological pathways involved in longevity. Second, we focused on the subset of the above genes that also had cross-validating genetic evidence in a genome-wide association study (GWAS) of depressive symptoms in aging (Figure 2). Third, we conducted a convergent functional genomics (CFG) analysis of this subset of genes for involvement in mood disorders and stress disorders, prioritizing our findings based on the whole body of work in the field to date (Figure 3). Fourth, in order to test whether *ANK3*, the top gene thus prioritized by CFG, is indeed involved in longevity/aging, we conducted studies with *C. elegans ANK3/unc-44* inactivating mutants (Figure 4), as well as gene-expression analyses (Supplementary Figure 2). Fifth, we conducted human genetic analyses with *ANK3* (Figure 5). Sixth, we conducted blood gene-expression analyses with *ANK3* (Figure 6) and a panel of the top genes (Supplementary Figure 1), showing their potential as biomarkers for age. Lastly, we sought to derive translational medicine insights by understanding the underlying biology, implications for disease and identification/repurposing of drugs. A mechanistic model is proposed (Figure 7).

MATERIALS AND METHODS

C. elegans studies

Mianserin-induced gene-expression changes. Mianserin-treated *C. elegans* whole-genome transcriptomic data were obtained as described by us.[7] Overall 6701 genes were changed in expression with at least nominal significance ($P < 0.05$, false discovery rate $< 10\%$) in mianserin vs water-treated worms. To ensure stringency in our analyses, we further applied to their *P* values a Bonferroni correction for number of genes in the genome (~21 035 genes), and carried forward in our analyses genes with a *P* value of $< 2.4 \times 10^{-6}$. A total of 1068 worm genes survived correction. Out of these, 971 were consistently upregulated or downregulated at the three time-points tested (days 3, 5 and 10).



b **Demographics**

CESD Score	No depressive symptoms controls CESD= 0	Depressive symptoms cases CESD ≥ 6	Overall (% with depressive symptoms)	
Number of Subjects	3338	239	3577 (6.7%)	
Female	2138	158	2296 (7.4%)	
Male	1200	81	1281(6.8%)	
Age mean	68.2	68.0	68.2	T-test for age between cases and controls
(SD)	(10.75)	(12.06)	(10.84)	0.838
Range	34-96	31-98	31-98	

Figure 2. Human GWAS. Identifying SNPs associated with depressive symptoms in an aging cohort using an extreme trait design. (**a**) Design of the study. (**b**) Demographics. CESD scale, Center for Epidemiological Studies Depression Scale; GWAS, genome-wide association study; HRS, Health and Retirement Study; SNP, single nucleotide polymorphism.

Assignment of human orthologs. To identify their corresponding orthologs we used OrthoList (www.greenwaldlab.org/ortholist/), a compendium of four orthology prediction programs, and manually searched for the human orthologs of the 971 worm genes. We only retained genes which had at least two out of the four prediction programs agreeing on assignments to human orthologs. We did that to ensure reliability of annotation, so we do not rely just on one software package/method. Out of 971 worm genes, 231 satisfied the above criteria. There were 347 human orthologs corresponding to these 231 worm genes. We used GeneCards (www.genecards.org) to confirm their gene symbol, name and chromosomal location.

Internal score for C. elegans data. We assigned the internal score to the 971 Bonferroni-corrected *C. elegans* genes according to the distribution of *P* values. The top 0.1% genes received an internal score of 4, top 5% received a score of 2 and remaining *C. elegans* genes received a score of 1. The corresponding human orthologs received same scores assigned to their *C. elegans* counterparts.

Human studies

GWAS for depressive symptoms in an ageing population. A new GWAS was conducted on data from 2006 Health and Retirement Study (HRS) wave 8, containing 30 671 subjects, which had previously been analyzed by us in a different fashion.[8] Subjects were assessed for depressive symptoms using the Center for Epidemiologic Studies Depression Scale comprising eight items. The score range is from 0 to 8, a score of 0 suggesting no depressive symptoms and a score of 6 and above suggesting severe depressive symptoms. The study sample only included

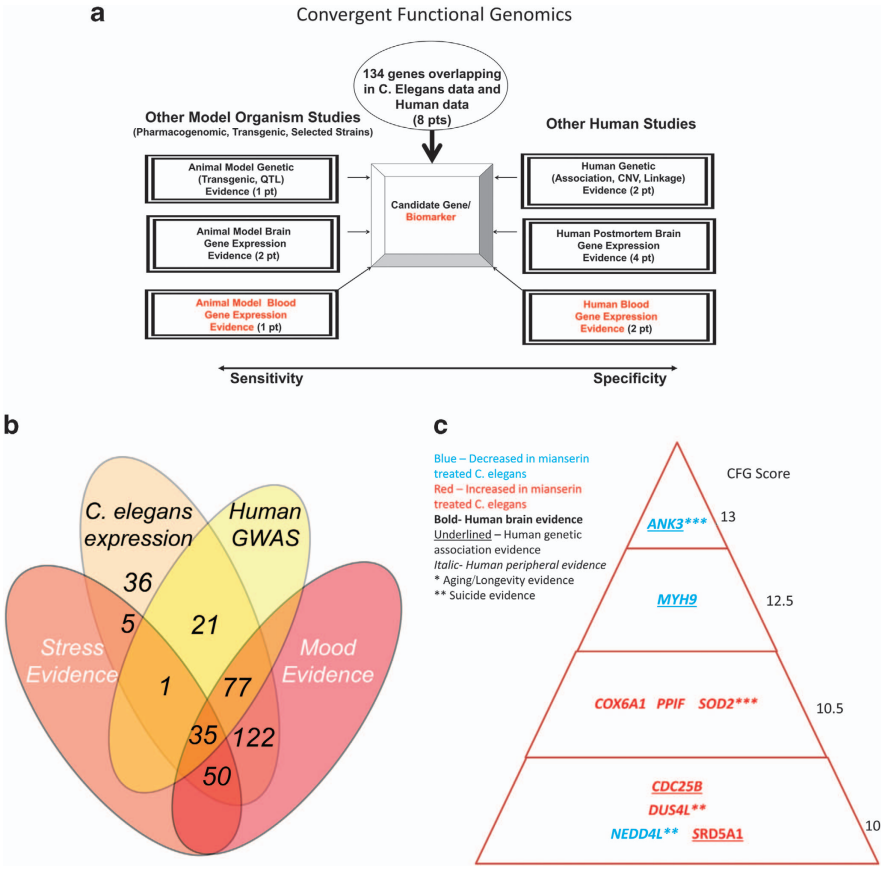


Figure 3. Convergent functional genomics. (**a**) Prioritizing the 134 genes that overlap between *C. elegans* discovery and human GWAS discovery, using convergent evidence for involvement in mood disorders and stress disorders. (**b**) Number of genes in the different evidentiary overlaps. (**c**) Top candidate genes for mood and stress-modulated longevity (CFG score ≥ 10). GWAS, genome-wide association study.

non-Hispanic Caucasians without a history of psychiatric or memory disorders. After balancing for age and gender, the study sample contained a total of 3577 subjects. We used an extreme trait design, wherein the control group consists of 3338 subjects without any depressive symptoms (1200 males, 2138 females) and cases consist of 239 subjects with severe depressive symptoms (81 males and 158 females). Genotype data was filtered using stringent quality control criteria. Association testing was performed using the Plink software package. Filtering resulted in a set of significant 56 499 single nucleotide polymorphisms (SNPs) (P value < 0.05).

Assignment of SNPs to genes. Initially the genes corresponding to the SNPs with $P < 0.05$ were identified using the annotation file from the UCSC Genome Browser website. A total of 8823 unique genes were identified. Thereafter, genes were cross checked using GeneCards to ensure that each gene symbol was current.

Internal score for the GWAS data. For the GWAS data the internal score was assigned based on the percentage of nominally significant SNPs (ratio of the number of significant SNPs over total number of SNPs tested per gene, multiplied by 100). We obtained a distribution of values. Genes in the top 0.1% of the distribution were assigned a score of 4, those in the top 5% were assigned a score of 2, whereas the remaining genes received a score of 1. We have successfully used a similar methodology in previous work.[9]

Convergent functional genomics

Databases: We have established in our laboratory (Laboratory of Neurophenomics, Indiana University School of Medicine, www.neurophenomics.info) manually curated databases of all the human gene expression (postmortem brain, blood and cell cultures), human genetics (association, copy number variations and linkage), and animal model gene expression and genetic studies published until now on psychiatric disorders. Only the findings deemed significant in the primary publication, by the study authors, using their particular experimental design and thresholds, are included in our databases. Our databases include only primary literature data and do not include review papers or other secondary data integration analyses to avoid redundancy and circularity. These large and constantly updated databases have been used in our CFG prioritization (Figure 3). For this study, data from 1556 papers on mood and on stress were present in the databases at the time of the CFG analyses (February 2015) (human: genetic studies—761, brain studies—226, peripheral fluids—311; non-human: genetic studies—41, brain studies—195, peripheral fluids—22).

Human postmortem brain gene-expression evidence: Converging evidence was scored for a gene if there were published reports of human postmortem data showing changes in expression of that gene or changes in protein levels in brains from subjects with mood or stress disorders.

Human blood and other peripheral tissue gene-expression data: Converging evidence was scored for a gene if there were published reports of human blood, lymphoblastoid cell lines,

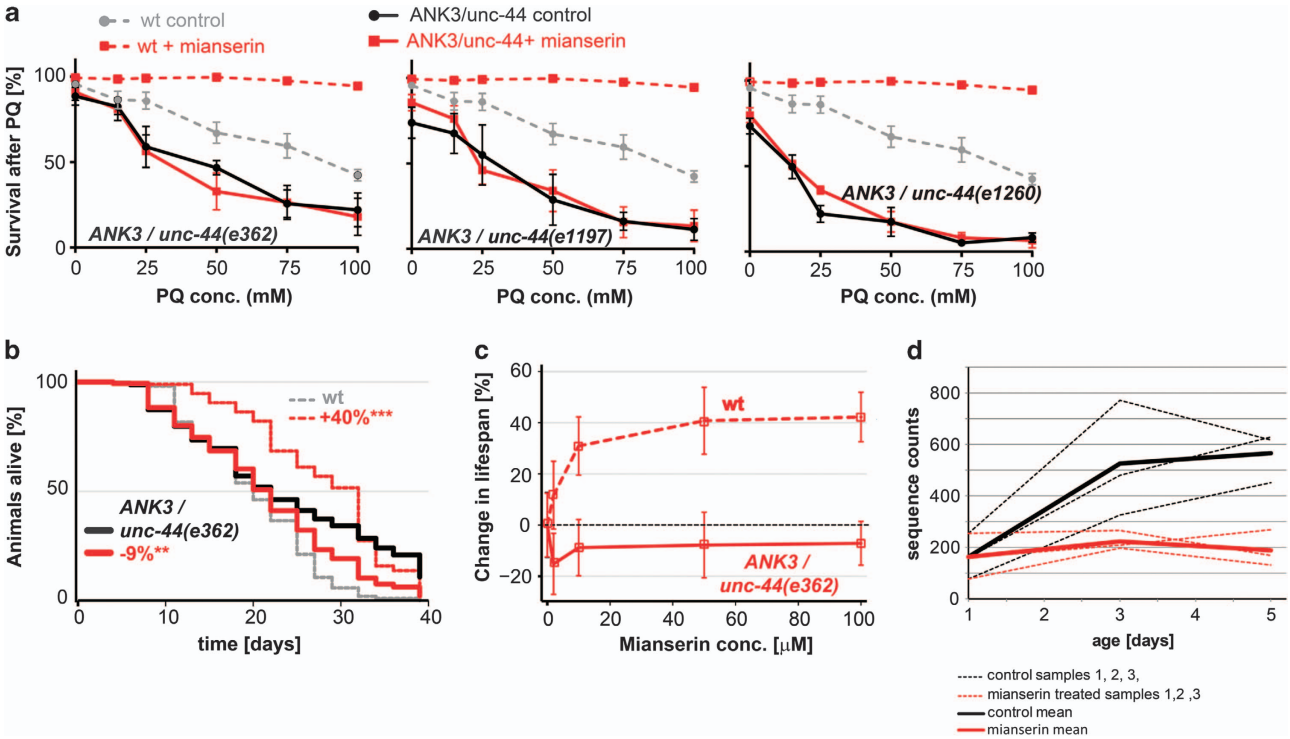


Figure 4. The antidepressant mianserin requires *ANK3/unc-44* to protect *C. elegans* from oxidative stress and to extend lifespan. (**a**) Mianserin-induced protection from oxidative stress requires *ANK3/unc-44*, the *C. elegans* homolog of mammalian *ANK3*. Wild-type (wt) N2 strain (dotted lines) or *ANK3/unc-44* mutants (bold lines), at day 1 adult stage, were treated with water (black) or 50 μM mianserin (red), followed by increasing concentrations of paraquat 5 days later. Survival of animals was determined 24 h after paraquat addition and plotted in (%) (*Y* axis) as a function of paraquat concentration (mM) (*X* axis). Parallel wt (N2) control experiments (dotted lines) are shown for each graph. Mianserin failed to increase resistance to oxidative stress in three independent alleles (*e362, e1197, e1260*) of *ANK3/unc-44*. All error bars show s.e.m. for 3 to 4 independent experiments. (**b**) Lifespan curves of wt and *unc-44(e362)* animals treated water or 50 μM mianserin. Graph shows animals alive (%) (*Y* axis) as a function of time (days) (*X* axis). Dotted lines represent wt (N2) animals and bold lines represent *unc-44(e362)* mutants. Black: solvent control; red: mianserin 50 μM. In wt animals, mianserin increases lifespan by +40%, whereas it does not (−9%) in *unc-44(e362)* mutant animals. Asterisks indicate *P* values (**$P < 0.01$, ***$P < 0.001$). (**c**) Graph shows mean increase in lifespan (%) (*Y* axis) as a function of mianserin concentration (μM) (*X* axis). Solid red line represents *unc-44(e362)* animals. Dotted red line represents the parallel control experiment of mianserin-treated wt (N2) animals. Error bars show s.d. for experimental replicates. No lifespan extension is observed in *ANK3/ unc-44(e362)* mutants at any mianserin concentration. (**d**) *ANK3/unc-44* expression with age.

cerebrospinal fluid or other peripheral tissue data showing changes in expression of that gene or changes in protein levels in participants with mood or stress disorders.

Human genetic evidence (association and linkage): To designate convergence for a particular gene, the gene had to have independent published evidence of association or linkage for mood disorders or stress disorders. For linkage, the location of each gene was obtained through GeneCards (http://www.genecards.org), and the sex averaged centimorgan location of the start of the gene was then obtained through http://compgen.rutgers.edu/mapinterpolator. For linkage convergence, the start of the gene had to map within 5 centimorgan of the location of a marker linked to the disorder.

Animal model brain and blood gene-expression evidence: For animal model brain and blood gene-expression evidence, we have used our own datasets,[10–12] as well as published reports from the literature curated in our databases.

Animal model genetic evidence: To search for mouse genetic evidence (transgenic and quantitative trait locus (QTL)) for our candidate genes, we utilized PubMed and the Jackson Laboratory database.

CFG scoring: For CFG analysis (Figure 3), the external cross-validating lines of evidence were weighted such that the findings in human postmortem brain tissue, the target organ, were prioritized over peripheral tissue findings and genetic findings, by giving them twice as many points. Human brain expression evidence was given 4 points, whereas human peripheral evidence was given 2 points, and human genetic evidence was given a maximum of 2 points for association, and 1 point for linkage. The scoring for the corresponding non-human lines of evidence were half of those in human (genetic—1 point, brain—2 points, peripheral—1 point). Each line of evidence was capped in such a way that any positive findings within that line of evidence result in maximum points, regardless if it came from mood or stress (as the two may be interrelated in some studies), and regardless of how many different studies support that single line of evidence (to avoid potential popularity biases). In addition to our external CFG score, we also prioritized genes based upon the internal score from the discovery analyses used to identify them, in mianserin-treated *C. elegans* and the depressive symptoms GWAS study. Genes identified in the discovery could receive a maximum of 8 points (4 from *C. elegans*, 4 from GWAS). Thus, the maximum possible total CFG score for each gene was 20 points (8 points for the internal score, 12 points for external CFG score) (Table 1 and Supplementary Table 2). The scoring system was decided on before the analyses were carried out. We sought to give more weight to external score as to internal in order to increase generalizability and avoid fit-to-cohort of the prioritized genes.[13] It has not escaped our attention that other ways of scoring the lines of evidence may give slightly different results in terms of prioritization, if not in terms of the list of genes *per se*. Nevertheless, we feel this simple scoring system provides a good

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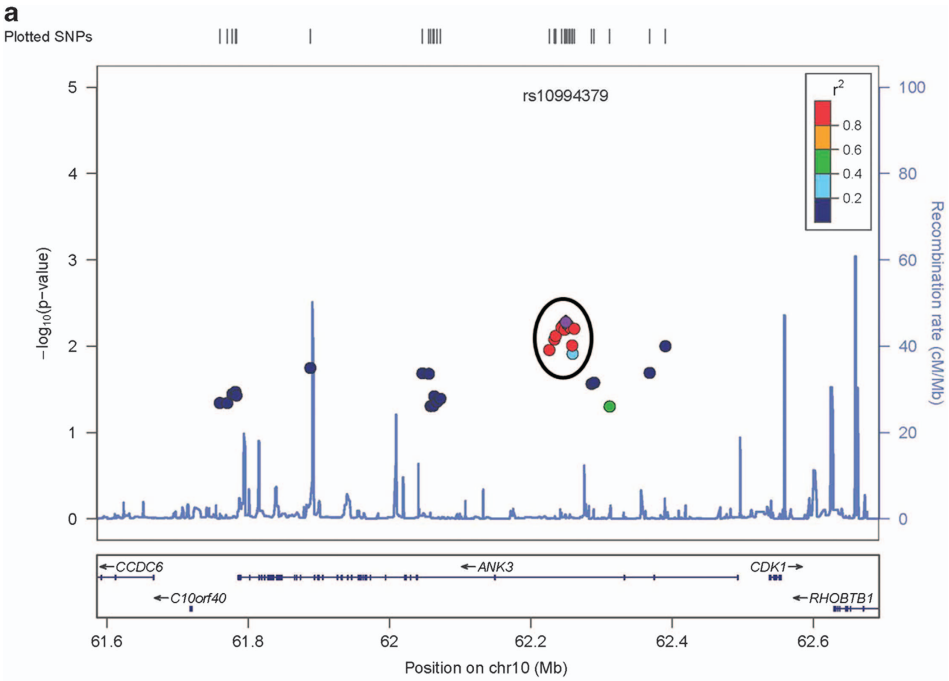


b

		Deceased n/avg. age at testing	Deceased n/avg. age at death	Deceased n (ANK3 SNP frequency)	Alive n/avg age at testing	Alive n (ANK3 SNP frequency)	OR Alive vs. Deceased ANK3 SNP	p-value Alive vs. Deceased ANK3 SNP t-test
Males	All	126/77.16	120/80.16	126(0.17)	676/77.15	676(0.24)	1.41	**0.031**
	Depressive Symptoms	18/77.65	17/79.70	18(0.22)	29/78.14	29(0.34)	1.55	0.2
	No Depressive Symptoms	108/77.07	103/80.24	108(0.16)	647/77.11	647(0.23)	1.44	**0.029**
Females	All	106/78.09	96/81.16	106(0.24)	750/78.10	750(0.26)	1.08	0.33
	Depressive Symptoms	19/76.25	18/79.02	19(0.26)	52/78.35	52(0.27)	1.04	0.46
	No Depressive Symptoms	87/78.49	78/81.65	87(0.23)	698/78.08	698(0.26)	1.13	0.31
Combined	All	232/77.58	216/80.61	232(0.2)	1426/77.65	1426(0.25)	1.25	**0.048**
	Depressive Symptoms	37/76.93	35/79.35	35(0.23)	81/78.28	81(0.3)	1.3	0.27
	No Depressive Symptoms	195/77.71	181/80.85	181(0.19)	1345/77.61	1345(0.25)	1.32	**0.043**

Figure 5. *ANK3* and survival. (**a**) Mapping of the nominally significant SNPs in *ANK3* for association with depressive symptoms in our GWAS. Circled is a cluster of SNPs around the most significant SNP (rs10994379; OR: 1.457, *P*-value: 0.0053). (**b**) *ANK3* association with survival, in the individuals who were alive at follow-up vs the individuals who died, using rs10994379 frequency (shown as a fraction of 1, whereas 1 is everybody in that group). GWAS, genome-wide association study; OR, odds ratio; SNP, single nucleotide polymorphism.

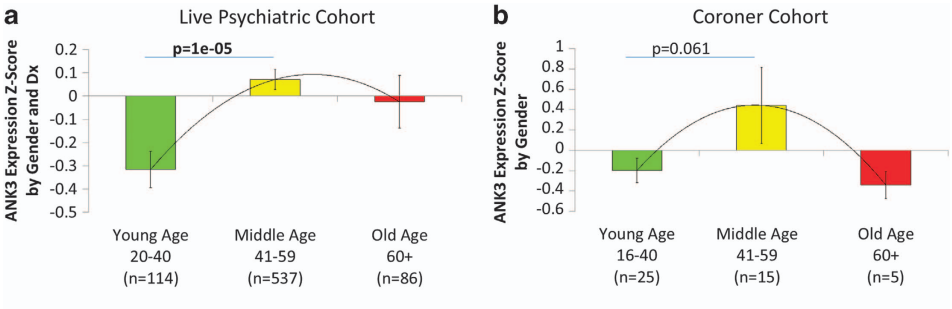
separation of genes based on internal discovery evidence and on external independent cross-validating evidence in the field (Figure 3). In the future, with multiple large datasets, machine learning approaches could be used and validated to assign weights to CFG.

Clock gene database

We compiled a database of genes associated with circadian function, by using a combination of review papers (Zhang *et al.*,[14] McCarthy and Welsh[15]) and searches of existing databases CircaDB (http://circadb.hogeneschlab.org), GeneCards (http://www.genecards.org) and GenAtlas (http://genatlas.medecine.univ-paris5.fr). Using the data we compiled from these sources, we identified a total of 1468 genes that show circadian functioning. We further classified genes into 'core' clock genes, that is, those genes that are the main engine driving circadian function ($n = 18$), 'immediate' clock genes, that is, the genes that directly input or output to the core clock ($n = 331$), and 'distant' clock genes, that is, genes that directly input or output to the immediate clock genes ($n = 1119$).

Genetic testing of *ANK3*

We tested the most significant SNP associated with depressive scores in *ANK3* (rs10994379; OR 1.457, *P* value 0.0053) for



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	Gender	Dx	n	ROC AUC Young vs. Middle Age	ROC p-value Young vs. Middle Age	OR Young vs. Middle Age	t-test Young vs. Middle Age
Live Psychiatric Cohort							
ANK3	Combined	Combined	651	**0.621**	**2.42e-05**	**4.441513**	**1e-05**
ANK3	Combined	Mood and stress (BP, MDD, Mood NOS, PTSD)	407	**0.605**	**0.0013**	3.824843	**0.002**
ANK3	Combined	BP	223	**0.604**	**0.012**	2.312123	**0.025**
ANK3	Combined	MDD	107	**0.680**	**.007**	6.883359	**0.002**
ANK3	Combined	Mood NOS	20	na	na	na	na
ANK3	Combined	PTSD	57	0.524	0.39	3.128619	0.42
ANK3	Combined	SZ	104	*0.618*	*0.079*	7.406621	**0.002**
ANK3	Combined	SZA	129	**0.722**	**0.0058**	6.204049	**8.37e-05**
ANK3	Combined	Psychosis NOS	11	na	na	na	na
ANK3	Males	Combined	519	**0.633**	**8.6e-05**	4.061966	**6.87e-05**
ANK3	Males	Mood and stress (BP, MDD, Mood NOS, PTSD)	311	**0.621**	**0.0017**	2.998416	**0.003**
ANK3	Males	BP	170	**0.602**	**0.032**	1.54726	**0.049**
ANK3	Males	MDD	80	**0.743**	**0.003**	7.34	**0.00045**
ANK3	Males	Mood NOS	20	na	na	na	na
ANK3	Males	PTSD	41	0.552	0.30	4.923682	0.32
ANK3	Males	SZ	94	0.608	0.12	8.154205	**0.005**
ANK3	Males	SZA	103	**0.784**	**0.01**	8.06947	**0.009**
ANK3	Males	Psychosis NOS	11	na	na	na	na
ANK3	Females	Combined	132	*0.591*	*0.056*	15.36415492	*0.051*
ANK3	Females	Mood and stress (BP, MDD, PTSD)	96	0.560	0.18	6.862507544	0.21
ANK3	Females	BP	53	0.601	0.12	10.48076	0.21
ANK3	Females	MDD	27	0.548	0.38	7.103472305	0.28
ANK3	Females	PTSD	16	0.417	0.71	0.5638	na
ANK3	Females	SZ	10	0.688	0.27	4	na
ANK3	Females	SZA	26	0.658	0.13	3.751275	**0.018**
Coroner Cohort							
ANK3	Combined	Suicide	40	0.613	0.12	0.445812	*0.061*
ANK3	Males	Suicide	33	0.674	0.057	0.368955	*0.059*
ANK3	Females	Suicide	7	0.417	0.69	1.333333	0.46

Figure 6. *ANK3* as a gene expression biomarker for biological age. *ANK3* gene expression in whole blood. (**a**) In live psychiatric patients. (**b**) In individuals who committed suicide. (**c**) Results by gender and diagnosis. *ANK3* expression levels are Z-scored by gender and diagnosis for the live psychiatric participants cohort, and Z-scored by gender for the coroner suicide cohort. Bold values are nominally significant. Italic values trend to significance. AUC, areas under the curve, for younger age vs middle age; BP, bipolar; MDD, major depressive disorder; mood NOS, mood disorder not otherwise specified; psychosis NOS, psychotic disorder not otherwise specified; OR, odds ratio; PTSD, posttraumatic stress disorder; ROC, receiver operating characteristic.

association with survival in our human GWAS cohorts (Figure 5). A one-tailed *t*-test with unequal variance was performed between subjects that were alive vs deceased at follow-up, which were carefully matched by gender and age at time of initial testing.

Human gene-expression studies

Cohorts. We derived our data from two cohorts: a live psychiatric participants cohorts, and a postmortem coroner's office cohort of individuals who died by suicide (Supplementary Table 1). The live psychiatric participants are part of a large longitudinal cohort that we are continuously collecting.[16] Participants are recruited from the patient population at the Indianapolis VA Medical Center and Indiana University School of Medicine through referrals from care providers, the use of brochures left in plain sight in public places and mental health clinics, and through word of mouth. All participants understood and signed informed consent forms detailing the research goals, procedure, caveats and safeguards. Participants completed diagnostic assessments by an extensive structured clinical interview—Diagnostic Interview for Genetic Studies—at a baseline visit, followed by up to six testing visits, 3–6 months apart or whenever a new psychiatric hospitalization occurred. At each testing visit, they received a series of psychiatric rating scales, and the blood was drawn. Our postmortem cohort consisted of a demographically matched cohort of 45 violent suicide completers obtained through the Marion County coroner's office (Supplementary Table 1B). We required a last observed alive

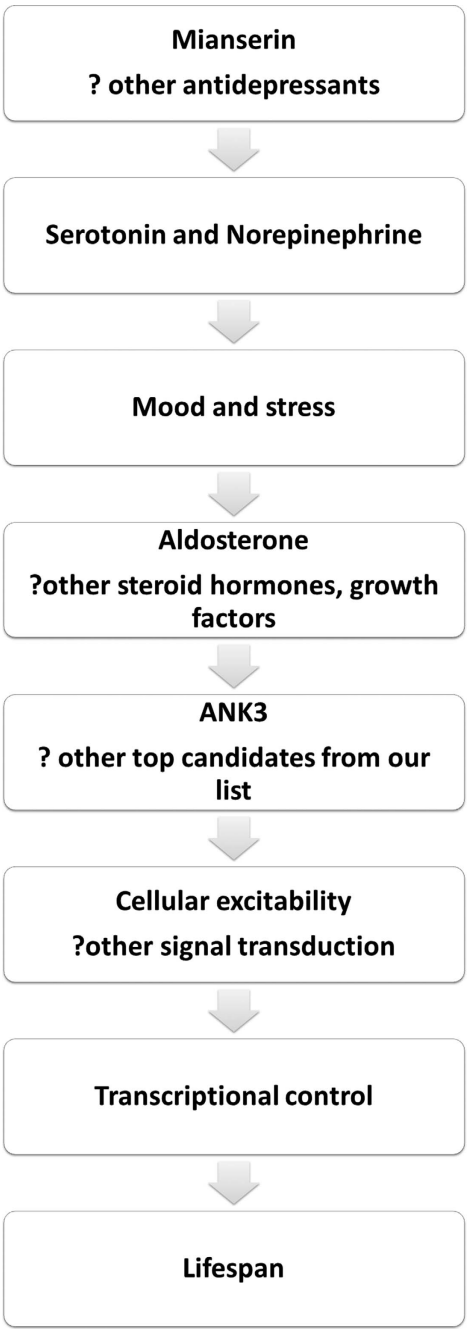

Figure 7. Proposed mechanistic cascade. *ANK3* may be a nodal point bringing together key biological processes related to cellular excitability, activity and connectivity.

postmortem interval of 24 h or less, and the cases selected had completed suicide by means other than overdose, which could affect gene expression. Next of kin signed informed consent at the coroner's office for donation of blood for research. The samples were collected as part of our INBRAIN initiative (Indiana Center for Biomarker Research in Neuropsychiatry).

In both cohorts, whole blood (10 ml) was collected in two RNA-stabilizing PAXgene tubes, labeled with an anonymized ID number, and stored at −80 °C in a locked freezer until the time of future processing. Whole-blood (predominantly lymphocyte) RNA was extracted for microarray gene expression studies from the PAXgene tubes, as previously described.[16]

Gene expression analyses

We imported all Affymetrix microarray data as .cel files into Partek Genomic Suites 6.6 software package (Partek, St Louis, MI, USA). Using only the perfect match values, we ran a robust multi-array analysis, background corrected with quantile normalization and a median polish probeset summarization, to obtain the normalized expression levels of all probesets for each chip. Robust multi-array analysis was performed independently for each of the diagnoses used in the study, to avoid potential artefacts due to different ranges of gene expression in different diagnoses. Then the participants' normalized data were extracted from these robust multi-array analyses and assembled for the different cohort analyses. Gene expression data was then *z*-scored by gender and diagnosis, to avoid potential artefacts due to different ranges of gene expression in different gender and diagnoses when combining cohorts, and to be able to combine different markers into a panel.

Statistical analyses

Receiver-operating characteristic analyses were calculated using the pROC function of the R studio, and double-checked using IBM SPSS Statistics 22. Diagnosis was converted to a binary call of 0 (middle and old age, above 40 years old) or 1 (young age, 20-40 years old) and entered as the state variable, with gene-expression levels entered as the test variable. In addition, Student's *t*-test was performed between young age (20–40 years old) and middle age (40–60 years old). For the top nine candidate genes of the effects of mood and stress on longevity (CFG score of 10 and above), a Pearson R correlation (one-tail) was calculated between age and gene-expression levels. On the Affymetrix HG-U133 Plus 2.0 GeneChip (Affymetrix, Santa Clara, CA, USA), there were 25 probesets total in the nine genes. Four out of five probesets in *ANK3*, and 16 probesets in five genes (*ANK3*, *PPIF*, *SOD2*, *NEDD4L*, *DUS4L*) (Supplementary Table 6), were inversely correlated with age compared with their direction of change in the mianserin-treated worms data, that is, if a gene was increased in expression in mianserin-treated worms, it should correlate inversely with age; if a gene was decreased in expression in mianserin-treated worms, it should correlate directly with age. The single best correlated probeset in each gene were selected for future analyses, for *ANK3* (Figure 6) and for the panel of five genes (BioM-5) (Supplementary Figure 1). The probesets were combined in the panel by computing the average of the *z*-scores of the increased markers minus the average of the *z*-scores of the decreased markers.

Pathway analyses

IPA (Ingenuity Systems, www.ingenuity.com, Redwood City, CA, USA), GeneGO MetaCore (Encinitas, CA, USA) and Kyoto Encyclopedia of Genes and Genomes (KEGG) (through the Partek Genomics Suite 6.6 software package) were used to analyze the biological roles, including top canonical pathways, and diseases, of the candidate genes resulting from our work, as well as to identify genes in our dataset that are the target of existing drugs (Table 2; Supplementary Table 4). We ran the pathway analyses together for all the 347 human orthologs, then for those of them that had some evidence for the human GWAS data ($n = 134$), then for those that had a total CFG score of 5 and above ($n = 67$), and finally for those that had a CFG score of 10 and above ($n = 9$) (Table 2; Supplementary Table 5).

Connectivity map analyses

To elucidate which drugs may induce a gene-expression signature similar to the nine top candidate genes for longevity from our current work (Supplementary Table 7), we utilized the Connectivity Map v2 (also known as cmap), which comprises a collection of

Table 1. Top candidate genes for mood and stress-modulated longevity ($n=9$, CFG score ≥ 10)

Human gene symbol/gene name/(worm gene)	*Direction of change in mianserin C. elegans*	*Discovery score*	*Human genetic evidence*	*Human brain expression evidence*	*Human peripheral expression evidence*	*Animal model genetic evidence*	*Animal model brain expression evidence*	*Animal model peripheral expression evidence*	*Prioritization total CFG score*
ANK3 ankyrin 3, node of Ranvier (ankyrin G) (unc-44)	D	*C. elegans* 1 Human 1	BP[40–44] PTSD[45]	(I) BP Brain[29]	(I) BP Blood[30] Lymphoblasts[31]	ANK3 KO[32]	(I) DBP Mice AMY [11] (D) DBP Mice Omega-3 fatty acids AMY[46]		13
MYH9 myosin, heavy chain 9, non-muscle (nmy-1)	D	*C. elegans* 1 Human 1	BP[47]	(D) MDD Choroid plexus[48]	(D) BP Blood[49]		(I) DBP Mice AMY [11] Stress AMY, HIP[50]	(I) Stimulants Blood[10] (D) DBP Mice Omega-3 fatty acids Blood[46]	12.5
PPIF peptidylprolyl isomerase F (cyn-7)	I	*C. elegans* 1 Human 1		(D) BP Brain[29,51] (D) PTSD PFC[52]	(I) Chronic Stress Blood[53]		(D) BP Brain[51]	(D) DBP Mice Omega-3 fatty acids Blood[46]	10.5
SOD2 superoxide dismutase 2, mitochondrial (sod-2)	I	*C. elegans* 1 Human 1	Stimulants[54] Linkage[55]	(D) MDD AMY and cingulate cortex [56] PFC[57]	(D) Antidepressants Blood[58]		(D)Depression Cingulate cortex[59]	(I) DBP Mice Omega-3 fatty acids Blood[46]	10.5
COX6A1 cytochrome c oxidase subunit VIa polypeptide 1 (tag-174)	I	*C. elegans* 1 Human 1	Linkage[60]	(D) BP, MDD PFC, cingulate cortex[61]	(I) Relaxation Response Blood[62]		(I) Mood Stabilizers Cerebral Cortex[63]	(I) DBP Mice Omega-3 fatty acids Blood[46]	10.5
SRD5A1 steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (F19H6.4)	I	*C. elegans* 1 Human 1	BP, Psychological stress[64]	(D) MDD Brain[29]			(D) PTSD AMY;HIP;PFC[65]		10
NEDD4L neural precursor cell expressed, developmentally downregulated 4-like, E3 ubiquitin protein ligase (Y92H12A.2)	D	*C. elegans* 1 Human 1	Linkage[66]	(D) BP Brain[29] PFC[67]	(D) BP Blood[68]		(D) DBP Mice Omega-3 fatty acids HIP (females)[46] (I) DBP Mice Omega-3 fatty acids NAC (females)[46]		10
CDC25B cell division cycle 25B (cdc-25.3)	I	*C. elegans* 1 Human 1	BP[47]	(D) BP Brain[29]	(D) Psychological Distress Blood[69] (I) Social Isolation Blood[70]				10
DUS4L dihydrouridine synthase 4-like (*S. cerevisiae*) (C45G9.2)	I	*C. elegans* 1 Human 1		(I) MDD PFC[71]	(D) BP Blood[68]		(D) Social Isolation HIP[72]		10

Abbreviations: AMY, amygdala; BP, bipolar; CP, caudate-putamen; (D), decreased in expression; HIP, hippocampus; (I), increased in expression; MDD, major depressive disorder; NAC, nucleus accumbens; PBMC, peripheral blood mononuclear cells; PFC, prefrontal cortex; PTSD, posttraumatic stress disorder.

genome-wide transcriptional expression data from cultured human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of functional connections between drugs, genes and diseases through the transitory feature of common gene-expression changes.[17] The cmap (http://www.broad.mit.edu/cmap) contains more than 7 000 expression profiles representing 1 309 compounds. We used the Affymetrix website to obtain the probesets ID corresponding to these nine top candidate genes in the HGU133A array chip that cmap used. We then used the quick query selection and uploaded the increased in expression genes probeset id in the up tag file, and the decreased in expression genes probeset id in the down tag file.

RESULTS

We first analyzed the human orthologs of genes that were significantly and consistently changed in expression by mianserin treatment in *C. elegans*, and identified biological pathways involved in longevity (Table 2). Notably, nicotine degradation, melatonin degradation, retinol metabolism, drug metabolism by cytochrome P450, chromatin modification and FGF-Erb signaling, were the top biological pathways identified.

Second, we focused on the subset of genes that also had genetic evidence in a GWAS of depressive symptoms in aging (Figure 2). We conducted a CFG analysis of those genes for involvement in mood disorders and stress disorders, prioritizing our findings based on the whole body of work in the field to date (Figure 3). Out of the 347 human orthologs of genes from the worm analysis, 134 had some nominal significant evidence for association with depressive symptoms in an aging population. Nine genes had a score of CFG 10 and above (⩾50% of the maximum possible CFG score of 20) (Table 1), and 67 genes had a CFG score of 5 and above (⩾25% of the maximum possible CFG score of 20) (Table 2). The top scoring gene from the CFG analysis was *ANK3* (Table 1).

Third, in order to validate whether *ANK3* is involved in longevity and aging, we conducted studies in *ANK3*/*unc-44* inactivating mutants in *C. elegans*, and demonstrate that they are longer lived than wt worms (Figure 4b). We also demonstrated using three different mutants that some *ANK3*/*unc-44* expression was necessary for the effects of mianserin on prolonging lifespan and survival in the face of oxidative stress, particularly in younger worms (Figures 4a and c). Wt *ANK3*/*unc-44* increases in expression with age in *C. elegans*, and is maintained at lower youthful levels by mianserin treatment (Figure 4d). These lower levels may be optimal in terms of longevity, offering a favorable balance between sufficient oxidative stress resistance in younger worms and survival effects in older worms.

We examined if genetic variants for depressive symptoms in *ANK3* are associated with longevity. Specifically, we focused on the strongest SNP from our GWAS analysis, rs10994379 (OR 1.457, *P* value 0.0053). Men with the risk allele for depressive symptoms had higher likelihood of survival (OR 1.41, *P* value 0.031), but not women (OR 1.08, *P* value 0.33). It is possible that SNPs that are associated with depressive symptoms may actually have a protective role in the non-depressed elderly in terms of lifespan, perhaps by reducing the level of activities that may be taxing in older people, or having some other non-mood related protective role. Consistent with that, individuals with bipolar disorder are known to have a shorter lifespans than individuals with depression.[1]

Fourth, we examined whether *ANK3*, by itself or in a panel with four other top CFG prioritized genes, acts as a blood gene-expression biomarker for age, in two independent cohorts, one of live psychiatric patients ($n=737$), and one of suicide completers from the coroner's office ($n=45$). We show significantly lower levels of *ANK3* expression in younger individuals, with another

Table 2. Biological pathways

A.	*Ingenuity pathways*				*KEGG pathways*			*GeneGO pathways*		
	#	*Top canonical pathways*	P *value*	*Ratio*	*Pathway name*	*Ratio*	*Enrichment* P *value*	*Process networks*	*Ratio*	P *value*
N = 347, *C. elegans* genes-corresponding unique human orthologs	1	Nicotine degradation III	1.42E–17	28.8% 17/59	Retinol metabolism	29.7956	1.15E–13	Transcription_Chromatin modification	5.686E–04	9/127
	2	Melatonin degradation I	2.03E–16	25.0% 17/68	Drug metabolism— cytochrome P450	27.5974	1.03E–12	Cardiac development_FGF_ErbB signaling	2.108E–03	8/124
	3	Nicotine degradation II	7.46E–16	23.3% 17/73	Metabolism of xenobiotics by cytochrome P450	25.6469	7.27E–12	Cell adhesion_Cell-matrix interactions	5.836E–03	10/211
	4	Superpathway of melatonin degradation	6.04E–15	20.7% 17/82	Drug metabolism— other enzymes	24.7258	1.83E–11	Development_Skeletal muscle development	1.767E–02	7/144
	5	Estrogen biosynthesis	9.71E–11	23.4% 11/47	Steroid hormone biosynthesis	22.9864	1.04E–10	Cardiac development_Wnt_beta-catenin, Notch, VEGF, IP3 and integrin signaling	2.160E–02	7/150
N = 134, genes that have GWAS evidence	1	Nicotine degradation III	7.44E–11	15.3% 9/59	Arachidonic acid metabolism	12.2523	4.77E–06	Development_Skeletal muscle development	1.237E–03	6/144
	2	Melatonin degradation I	2.79E–10	13.2% 9/68	Metabolism of xenobiotics by cytochrome P450	12.2158	4.95E–06	DNA damage_MMR repair	1.451E–03	4/59
	3	Nicotine degradation II	5.36E–10	12.3% 9/73	Drug metabolism— cytochrome P450	11.5538	9.60E–06	Cardiac development_Wnt_beta-catenin, Notch, VEGF, IP3 and integrin signaling	1.526E–03	6/150
	4	Superpathway of melatonin degradation	1.55E–09	11.0% 9/82	Retinol metabolism	11.4604	1.05E–05	Cardiac development_FGF_ErbB signaling	3.705E–03	5/124
	5	Bupropion degradation	5.23E–07	18.5% 5/27	Starch and sucrose metabolism	11.3695	1.15E–05	Transcription_Chromatin modification	4.104E–03	5/127
N = 67, genes CFG ≥ 5	1	Mitochondrial dysfunction	1.80E–05	3.2% 6/188	Linoleic acid metabolism	10.7199	2.21E–05	Signal transduction_Androgen receptor nuclear signaling	4.711E–03	4/126
	2	Bupropion degradation	6.57E–05	11.1% 3/27	Arachidonic acid metabolism	7.58419	0.000508	Transcription_Chromatin modification	4.845E–03	4/127
	3	Acetone degradation i (to methylglyoxal)	1.21E–04	9.1% 3/33	Glycine, serine and threonine metabolism	7.06642	0.000853	Development_Skeletal muscle development	7.537E–03	4/144
	4	Cysteine biosynthesis/ homocysteine degradation	2.31E–04	25.0% 2/8	Viral myocarditis	6.46753	0.001553	Transport_Synaptic vesicle exocytosis	1.468E–02	4/175
	5	Estrogen biosynthesis	3.49E–04	6.4% 3/47	Linoleic acid metabolism	10.7199	2.21E–05	Cytoskeleton_Actin filaments	1.497E–02	4/176
N = 9, genes CFG ≥ 10	1	Mitochondrial dysfunction	1.97E–03	1.1% 2/188	Huntington's disease	7.03869	0.000877	Cytoskeleton_Actin filaments	1.107E–03	3/176
	2	Superoxide radicals degradation	3.64E–03	10.0% 1/10	Parkinson's disease	4.76458	0.008526	Signal transduction_Androgen receptor nuclear signaling	1.025E–02	2/126
	3	Androgen biosynthesis	9.43E–03	3.8% 1/26	Aldosterone—regulated sodium reabsorption	2.98928	0.050324	Cardiac development_Role of NADPH oxidase and ROS	1.154E–02	2/134
	4	Cell cycle: G2/M DNA damage checkpoint regulation	9.43E–03	2.0% 1/49	Androgen and estrogen metabolism	2.98358	0.050611	Cell cycle_Mitosis	2.002E–02	2/179
	5	Mitotic roles of polo-like kinase	2.38E–02	1.5% 1/66	Steroid hormone biosynthesis	2.53105	0.079575	Cytoskeleton_Regulation of cytoskeleton rearrangement	2.088E–02	2/183

Abbreviations: CFG, convergent functional genomics; GWAS, genome-wide association study.

decrease in levels occurring in older age. *ANK3* also increases in expression with age in worms (Figure 4d). Importantly, *ANK3* was previously reported to be overexpressed in fibroblasts from patients with Hutchinson–Gilford progeria syndrome, a form of accelerated aging. We also show similar results for a panel of five top genes (Supplementary Figure 1; Supplementary Table 6).

Lastly, we sought to derive translational medicine insights. Previous work by our group had shown that *ANK3* was increased in expression in the amygdala of a mouse model of mood disorders and stress,[11] and that *ANK3* was decreased in expression in that model by treatment with the omega-3 fatty acid DHA (docosahexaenoic acid), similar to the effects of mianserin in worms. A number of other top scoring genes (*MYH9*, *SOD2*, *COX6A1*, *NEDD4L*, *SYT1*, *TROVE2*, *H3F3A*, *PEBP1*, *PLA2G6*, *SCD5*) had evidence of modulation by DHA in the same direction with mianserin (Supplementary Table 4), suggesting that omega-3 fatty acids may have longevity promoting effects as well. In fact, one of the top biological pathways is linoleic acid metabolism, related to omega-3 fatty acids (Table 2).

A number of top biomarkers identified by us have biological roles that are related to the circadian clock. To be able to ascertain all the genes in our dataset that were circadian and do estimates for enrichment, we compiled from the literature a database of all the known genes that fall into these three categories: core clock, immediate input or output and distant input or output, numbering a total of 1468 genes. Using an estimate of about 21 000 genes in the human genome, that gives about 7% of genes having some circadian pattern. Out of our 67 top longevity biomarker genes, 11 had circadian evidence (16.4%) (Supplementary Table 2), suggesting an over twofold enrichment for circadian genes. Circadian clock abnormalities are related to mood disorders[11,15] and neurodegenerative disorders;[18] sleep abnormalities have been implicated in aging.[19]

We have identified a series of biomarkers that seem to be changed in expression opposite direction in longevity vs in Alzheimer disease (Supplementary Table 3). These biomarkers could potentially suggest targets for early intervention and preventive approaches. COX6A1 (cytochrome c oxidase subunit VIa polypeptide 1, the terminal enzyme of the mitochondrial respiratory chain), and CYB5R3 (cytochrome b5 reductase 3, which functions in desaturation and elongation of fatty acids, in cholesterol biosynthesis, and in drug metabolism), are increased in longevity, and decreased in blood of Alzheimer disease individuals.[20] KAT2B (K(lysine) acetyltransferase 2B, which has histone acetyl transferase activity with core histones and nucleosome core particles, indicating that this protein plays a direct role in transcriptional regulation) is increased in longevity and decreased in the hippocampus of Alzheimer diseases individuals.[21]

One of the other biomarkers increased in longevity is SRD5A1 (steroid-5-alpha-reductase alpha polypeptide 1). Inhibitors of this enzyme, such as those used in prostate disorders, lead to androgenic blockade, which has been associated with a higher rate of Alzheimer disease.[22] Interestingly, one of the top biological pathways identified by us is androgen receptor signaling (Table 2).

We have also identified a series of biomarkers that seem to be changed in opposite direction in longevity vs suicide: *ANK3*, *SOD2*, *DUS4L*, *NEDD4L*, *MYH11*, *NAV3*, *YIPF5* and 15 other genes (Supplementary Table 3). In particular, *EPHX1*, increased in longevity, is decreased in both brain[23] and blood[24] in suicidality. The other genes that have blood evidence in suicide in opposite direction to longevity are: *ANK3*, *DUS4L*, *NEDD4L*, *MYH11*, *NAV3*, *YIPF5*, *TROVE2*, *CLASP2*, *MSH2*, *POLH*, *FAM184A*, *CBS*, *CYB5R3*, *CYP2C9*, *and NLGN2*. Such genes may be blood biomarkers for a biological switch implicated in survival, that is, a 'life switch'.

Pharmacogenomics and therapeutics

We have identified a series of biomarkers that seem to be changed in the same direction in longevity vs in treatments with mood stabilizing agents, such as lithium, valproate and omega-3 fatty acids (Supplementary Table 4). These biomarkers could potentially be used to stratify patients to different treatment approaches, and monitor their response. *COX6A1, SYT1, TROVE2 and NLGN2* are changed in expression by two of these three treatments, suggesting they may be core to the mood and longevity mechanisms of these drugs. *MYH9, SOD2, COX6A1, TROVE2, H3F3A, PLA2G6* and *PEBP1* may be useful blood pharmacogenomic markers of response to omega-3 fatty acids. Two existing drugs used for other indications have been identified as targeting top longevity biomarkers identified by us (Supplementary Table 4), and them or their derivatives could potentially be repurposed for testing for prolonging life: quinacrine (inhibiting *PLA2G6*), and sulfinpyrazone (inhibiting *ABCC1*).

In addition, Connectivity Map analyses[17] identified compounds that induce gene-expression signatures that are similar to those of the top nine mood and stress-modulated longevity genes (Supplementary Table 7), and might generate leads and/or be tested for use in prolonging lifespan: antidiabetic medications (troglitazone, gliquidone, pioglitazone, rosiglitazone), immunosuppressant/anti-transplant rejection medications with known longevity effects across species (sirolimus/rapamycin, mycophenolic acid), nootropic (piracetam) and non-drug flavonoid antioxidant/vitamin compounds (quercetin, resveratrol, ergocalciferol/vitamin D). Known mood modulating drugs identified by the Connectivity Map analyses are: antidepressants (minaprine, amoxapine), antihistamines (homochlorcyclizine), calcium-channel blockers (nifedipine) and female sex hormone-like compounds (diethylstilbestrol, estradiol). Of note, females tend to live longer than males in humans, and estradiol has direct prior experimental evidence of extending lifespan in worms.[25]

We have also looked using Connectivity Map at compounds that have similar gene-expression signatures to the 22 genes that are changed in opposite direction in longevity and suicide, and identified additional flavonoid antioxidants (apigenin, luteolin, acacetin) and vitamins (vitamin K, folic acid), along with resveratrol, estradiol, antidiabetics and antineoplastics. Moreover, some of the genes in this 'life switch' are modulated by omega-3 fatty acids, lithium and valproate (Supplementary Table 8).

DISCUSSION

ANK3, the top gene at the overlap of longevity, mood and stress identified by our convergent approach, is a scaffolding protein, involved in assembly and trafficking of receptors and channels, notably at the nodes of Ranvier and in the synaptic compartment,[26,27] with a strong genetic association with several psychiatric disorders. It has been implicated in anhedonia, stress, novelty seeking and cognition in humans. *ANK3* is a top genome-wide significant hit from GWAS studies of bipolar disorder.[28] Other work in the field has identified *ANK3* as increased in expression in individuals with bipolar disorder, in brain[29] and blood.[30,31] Mice with deletions of *ANK3* display a hyperactive phenotype, that is responsive to treatment with the mood stabilizer lithium, and switches to a more inactive phenotype in response to chronic stress, as described in elegant studies by Petryshen and colleagues.[32] At a cellular level, over-expression of *ANK3* increases lysosomal-mediated down-regulation of cell-surface receptors.[33] *ANK3* has been shown to regulate the Wnt pathway signaling and cell proliferation.[34] *ANK3* has also been shown to be regulated by aldosterone, and in turn to regulate the activity of sodium channels that promote sodium retention.[35] Sodium homeostasis may be a very primitive cellular mechanism that has evolutionarily

been co-opted for increasingly complex organismal functions and responses, including neuronal excitability.

Our data shows that *ANK3* seems to be expressed at lower levels in younger individuals (worms and humans) (Figures 4d, 6a and b), and that mianserin may have longevity effects primarily by maintaining *ANK3* at lower/youthful levels (Figure 4), which in turn leads to a tighter transcriptional control (Figure 7) and prevents transcriptional drift.[7] The observation that inactivating mutations in *ANK3*/*unc-44* cause hypersensitivity to oxidative stress in young animals but extend lifespan later in life suggest *ANK3*/*unc-44* may be an example of antagonistic pleiotropy.[36] *ANK3*/*unc-44* provides a fitness advantage in the young organism, but its increased expression becomes detrimental in older animals. Interestingly, the curve for *ANK3* expression with age might not be linear but rather bell-shaped, with lower levels of *ANK3* again occurring in older age (Figure 6). Whether that represents a survival effect or an age-related effect is unclear at this point. The effects of *ANK3* in older age in general, and in Alzheimer disease in particular, are an area of future exploration by our group.

The ability of *ANK3* (Figure 6), and of our panel of top biomarkers (BioM-5) (Supplementary Figure 1) to distinguish between younger age and middle age, while significant overall, seems to be even better in certain gender and diagnostic subgroups (males and females with schizoaffective disorder and schizophrenia, males with depression), suggesting avenues for personalized medicine, potential medication effects, as well as potential biological severity and burden of disease. Our human blood gene-expression data are in a psychiatric cohort and a coroner suicide cohort, populations where *ANK3* and other biomarkers might be more strongly modulated by mood and stress effects. Additional normative studies in non-psychiatric populations are needed for the magnitude of the effects with age of *ANK3*, and BioM-5. They may uncover utility for our biomarkers to contribute to a biological age score, as opposed to a chronological age. For example, they may be shifted in a negative direction in individuals exposed to mood and stress disorders. Consistent with that, our coroner cohort, composed of individuals who committed suicide and presumably were exposed to more severe negative mood and stress, appears shifted compared to our live psychiatric cohort (lower OR between young and middle age). It would also be interesting as part of future work to correlate the levels of our candidate biomarkers with telomere length, a known stress-responsive marker of aging.[37]

The probeset used for *ANK3* maps to protein coding transcripts of *ANK3* (Supplementary Figure 2), which is a very complex gene. As a caveat, our gene-expression data was determined using probesets for the genes that showed best concordance with the worm directionality in our psychiatric patients test cohort. However, these probesets were enriched in the complete list of probsets from the Affymetrix chip (Supplementary Table 6). Moreover, the results were very similar in the independent coroner cohort.

Independent of this study, we recently observed somewhat similar effects to *ANK3*/*unc-44* for mutants of SYT1/snt-1,[7] one of our top genes from this study (Supplementary Table 2). It would be interesting in the future to test other mutants of top genes identified by us, and see if they converge on synaptic pathology.

Other biological insights (Alzheimer disease implications, circadian clocks, longevity/suicide 'life switch'), as well as pharmacogenomics and therapeutics leads, notably antidiabetic/insulin modulating drugs and flavonoid antioxidant/vitamin compounds, are listed in the Results section. Of note, as reassuring positive controls, the gene-expression signature of our top genes for mood and stress modulated longevity has similarity with the gene-expression signature of resveratrol, a known longevity promoting compound, and of sirolimus/rapamycin, an anti-transplant rejection medication with known longevity effects across species (Supplementary Table 7).[38] Conversely, the mechanistic target of rapamycin pathway it targets was a top pathway identified in previous work by us on suicide biomarkers, pointing to its role as a potential life/death switch.[16]

Mitochondrial dysfunction was the top biological pathway where our top candidate genes for mood and stress-modulated longevity mapped (Table 2). Over the last decade, accumulating evidence has suggested a causative link between mitochondrial dysfunction and major phenotypes associated with aging. Besides free radicals, other possible mechanisms, including insulin signaling and mechanistic target of rapamycin (mTOR) pathways connect mitochondria to aging.[39]

The fact that *ANK3* and other genes are changed in expression in opposite directions in longevity vs suicide datasets is of speculative evolutionary interest in terms of a 'life switch'. One essential program that every organism might have is an inherent will to survive, a program that must be biologically encoded. That program may be inactivated/switched off, that is, a breakdown of the drive to survive may occur in suicide. Suicide is, *de facto*, a form of reduced longevity. Such genes may be tested in the future for use in a polygenic gene-expression 'viability score', to quantify the likelihood of longevity vs suicide in psychiatric patients (and non-psychiatric individuals), as well as to monitor response to treatments in individuals at risk.

Overall, we propose a model, whereas positive or negative mood and stress responses, reflecting the organism's state of health and perception of the environment as favorable or hostile, and their influence on behaviors, may be involved in the active modulation of lifespan, with *ANK3* and other genes as mediators. In particular, *ANK3* may be a nodal point in the regulation of overall cellular excitability, signal transduction and transcriptional control (Figure 7).

Note

Supplementary information is available at the journal website and from the Niculescu Laboratory website (www.neurophenomics.info).

CONFLICT OF INTEREST

The authors declare no conflict of interest. ABN, MP, DRS and AJS are listed as inventors on a patent application being filed by Indiana University and Scripps.

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AUTHOR CONTRIBUTIONS

ABN, MP, DRS and AJS designed the study, and ABN wrote the manuscript. SR, DFL, KN, NJ, KDA and HLN conducted experiments and analyzed the data. All authors discussed the results and commented on the manuscript.

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Supplementary Information accompanies the paper on the *Molecular Psychiatry* website (http://www.nature.com/mp).

Molecular Psychiatry

Supplementary Information

Figure S1 Panel of top biomarkers as a potential gene expression measure for biological age. 5 out of the top 9 genes had gene expression changes with age in the same direction as in mianserin-treated C. elegans (Table S6). BioM-5 is a panel of these genes (ANK3, PPIF, SOD2, NEDD4L, DUS4L). A. BioM-5 expression across age groups in the live psychiatric cohort B. BioM-5 expression across age groups in the coroner cohort. C. Results by gender and diagnosis. ROC- Receiver operating characteristic, AUC- areas under the curve, for younger age vs. middle age. OR- Odds ratio. BP- bipolar disorder; MDD- major depressive disorder; SZ- schizophrenia; SZA- schizoaffective disorder; PTSD- post-traumatic stress disorder; Mood NOS- mood disorder not otherwise specified; Psychosis NOS- psychotic disorder not otherwise specified.

Figure S1.

C.

	Gender	Dx	n	ROC AUC Young vs. Middle Age	ROC p-value Young vs. Middle Age	OR Young vs. Middle Age	t-test Young vs. Middle Age
Live Psychiatric Cohort							
BioM5	Combined	Combined	651	**0.622**	**2.24e-05**	4.487795	**1.78e-05**
BioM5	Combined	Mood and stress (BP, MDD, Mood NOS, PTSD)	407	**0.607**	**0.0011**	3.269142	**0.001**
BioM5	Combined	BP	223	**0.596**	**0.018**	1.749534	**0.025**
BioM5	Combined	MDD	107	*0.596*	*0.095*	20.4177	0.082
BioM5	Combined	Mood NOS	20	na	na	na	na
BioM5	Combined	PTSD	57	**0.676**	**0.018**	1.748024	**0.013**
BioM5	Combined	SZ	104	**0.717**	**0.0046**	7.522054	**0.017**
BioM5	Combined	SZA	129	**0.655**	**0.039**	7.596345	**0.019**
BioM5	Combined	Psychosis NOS	11	na	na	na	na
BioM5	Males	Combined	519	**0.593**	**0.0043**	3.901596	**0.003**
BioM5	Males	Mood and stress (BP, MDD, Mood NOS, PTSD)	311	**0.601**	**0.007**	2.713137	**0.008**
BioM5	Males	BP	170	0.559	0.14	0.989707	0.18
BioM5	Males	MDD	80	**0.657**	**0.038**	11.61279	**0.03541**
BioM5	Males	Mood NOS	20	na	na	na	na
BioM5	Males	PTSD	41	**0.684**	**0.031**	1.384538	**0.017**
BioM5	Males	SZ	94	**0.666**	**0.033**	8.678322	0.061
BioM5	Males	SZA	103	0.447	0.67	2.376518	0.582
BioM5	Males	Psychosis NOS	11	na	na	na	na
BioM5	Females	Combined	132	**0.701**	**0.00022**	4.917807	**0.00037**
BioM5	Females	Mood and stress (BP, MDD, PTSD)	96	**0.625**	**0.029**	7.020574	**0.043**
BioM5	Females	BP	53	**0.691**	**0.013**	2.069784	**0.012**
BioM5	Females	MDD	27	0.452	0.64	0.013337	0.702
BioM5	Females	PTSD	16	0.667	0.19	8.155267	0.25
BioM5	Females	SZ	10	**1**	**0.022**	3.999996	**0.026**
BioM5	Females	SZA	26	**0.883**	**0.0017**	6.405171	**2.01e-05**
Coroner Cohort							
BioM5	Combined	Suicide	40	**0.773**	**0.0018**	0.521546	**0.007**
BioM5	Males	Suicide	33	**0.798**	**0.0025**	0.41894	**0.014**
BioM5	Females	Suicide	7	0.75	0.2	1.333333	0.167

Figure S2. ANK3 probeset used (239726_at, boxed; see also Table S6) and its mapping to the different ANK3 isoforms.

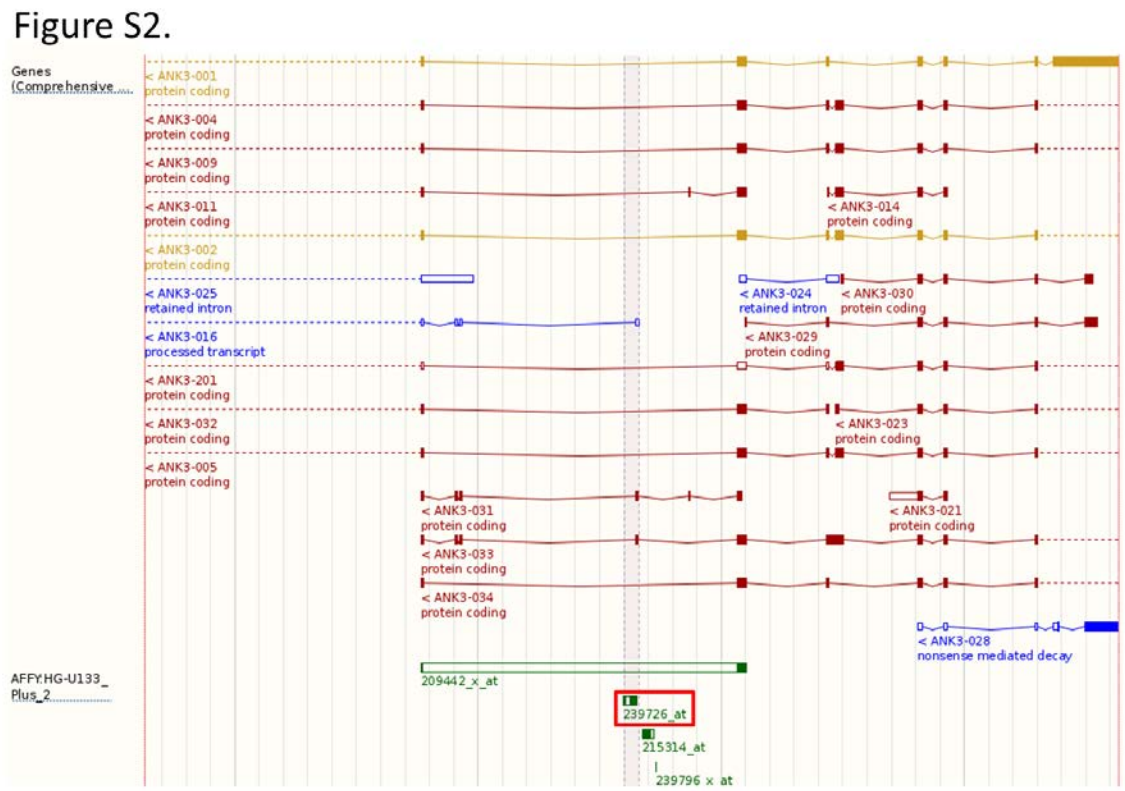

Table S1. Cohorts demographics

A. Live psychiatric patients

Group Avg. (SD)	N Subjects (Testing Visits)	Gender Subjects (Testing Visits)	Diagnosis Subjects (Testing Visits)
Young Age **20-40** 31.7 (5.96)	53 (114)	Males:39 (79) Females:14 (35)	BP:24 (52) MDD:8 (19) SZA:5 (12) SZ:7 (14) PTSD:9 (17)
Middle Age **41-59** 51.24 (4.95)	214 (537)	Males:173 (440) Females:41 (97)	BP:61 (171) MDD:37 (88) MOOD NOS:7 (20) SZA:50 (117) SZ:35 (90) PSYCH NOS:6 (11) PTSD:18 (40)
Old Age **60+** 62.08 (2.18)	34 (86)	Males: 28 (72) Females: 6 (14)	BP:9 (27) MDD:6 (15) SZA:9 (21) SZ:8 (19) PTSD:2 (4)

B. Coroner suicide cases (n=45).

Group Avg. (SD)	N	Gender	Diagnosis
Young Age 20-40 27.44 (7.76)	25	Males:22 Females:3	Non Psych=15 MDD=7 BP=1 SZ=1 ADHD=1
Middle Age 41-59 53.4 (4.90)	15	Males:11 Females:4	Non Psych=6 MDD=8 BP=1
Old Age 60+ 68.8 (4.21)	5	Males: 5	Non Psych=2 MDD=1 AX=1 Alcoholism=1

Table S2. Top candidate genes for mood and stress-modulated longevity: mood and stress evidence (n=67, CFG≥5).

Human Gene Symbol/Gene Name/ (Worm gene)	Direction of Change In Mianserin C. elegans	Discovery	Human genetic evidence	Human Brain expression evidence	Human peripheral expression evidence	Nonhuman genetic evidence	Nonhuman Brain expression evidence	Nonhuman peripheral expression evidence	Prioritization Total CFG Score	Circadian Clock Role
ANK3 ankyrin 3, node of Ranvier (ankyrin G) (unc-44)	D	C. elegans 1 Human 1	**BP** [1 2 3 4 5] **PTSD** [6]	(I) **BP** Brain [7]	(I) **BP** Blood [8] lymphoblast [9]	ANK 3 KO[10]	(I) **DBP NST Mice** AMY [11] (D) **DBP Mice** DHA AMY [12]		13	
MYH9 myosin, heavy chain 9, non-muscle (nmy-1)	D	C. elegans 1 Human 1	**BP** [13]	(D) **MDD** Choroid plexus [14]	(D) **BP** Blood [15]		(I) **DBP ST Mice** AMY [11] **Stress** AMY, HIP [16]	(I) **Stimulants** Blood [17] (D) **DBP Mice** DHA Blood [12]	12.5	
COX6A1 cytochrome c oxidase subunit VIa polypeptide 1 (tag-174)	I	C. elegans 1 Human 1	Linkage [18]	(D) **BP, MDD** DLPFC, ACC [19]	(I) **Relaxation Response** Blood [20]		(I) **Mood Stabilizers** Cerebral Cortex [21]	(I) **DBP Mice** DHA Blood [12]	10.5	
PPIF peptidylprolyl isomerase F (cyn-7)	I	C. elegans 1 Human 1		(D) **BP** Brain [7] [22] (D) **PTSD** DLPFC BA46 [23]	(I) **Chronic Stress** Blood [24]		(D) **BP** Brain [22]	(D) **DBP Mice** DHA Blood [12]	10.5	
SOD2 superoxide dismutase 2, mitochondrial (sod-2)	I	C. elegans 1 Human 1	**Stimulants** [25] Linkage [26]	(D) **MDD** AMY and cingulate cortex [27] FPC [28]	(D) **Antidepressants** Blood [29]		(D) **Depression** Cingulate cortex [30]	(I) **DBP Mice** DHA Blood [12]	10.5	
CDC25B cell division cycle 25B (cdc-25.3)	I	C. elegans 1 Human 1	**BP** [13]	(D) **BP** Brain [7]	(D) **Psychological Distress** Blood [31] (I) **Social Isolation**				10	

					Blood [32]					
DUS4L dihydrouridine synthase 4-like (S. cerevisiae) (C45G9.2)	I	C. elegans 1 Human 1		(I) **MDD** DLPFC [33]	(D) **BP** Blood [34]		(D) **Social Isolation** HIP DG [35]		10	
NEDD4L neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase (Y92H12A.2)	D	C. elegans 1 Human 1	Linkage [36]	(D) **BP** Brain [7] DLPFC Broadmann Area 9 [37]	(D) **BP** Blood [34]		(D) **DBP Mice** DHA HIP (females) [12] (I) **DBP Mice** DHA NAC (females) [12]		10	Immediate output
SRD5A1 steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (F19H6.4)	I	C. elegans 1 Human 1	**BP, Psychological Stress** [38]	(D) **MDD** Brain [7]			(D) **PTSD** AMY,HIP,PFC [39]		10	
CROCC ciliary rootlet coiled-coil, rootletin (Ifi-1)	D	C. elegans 1 Human 1	Linkage [40]	(I) **BP and MDD** Pituitary [41]	(D) **MDD** Blood [42]				9	
FAM91A1 family with sequence similarity 91, member A1 (F33H2.2)	I	C. elegans 1 Human 1	Linkage [43]	(I) **MDD** AMY and cingulate cortex [27]			(I) **Depression** HIP [44]		9	
JPH3 junctophilin 3 (jph-1)	D	C. elegans 1 Human 1	Linkage [45]	(D) **BP** Brain [7]			(D) **Stress** Hypothalamus [46]		9	
MACROD1 MACRO domain containing 1 (B0035.3)	I	C. elegans 1 Human 1	Linkage [47]	(D) **PTSD** DLPFC BA46 [23]	(D) **BP** Blood [34]				9	
MYH11 myosin, heavy chain 11, smooth muscle (nmy-1)	D	C. elegans 1 Human 1		(D) **MDD** Choroid plexus [14]	(D) **BP** PBMC [48]		(D) **Mood Stabilizers** AMY [49]		9	
NAV3 neuron	D	C. elegans 1		(D) **BP**			(I) **DBP NST**		9	

navigator 3 (unc-53)		Human 1	Linkage [50]	Brain [7]			**Mice** AMY [11] (D) **Mood Stabilizers** AMY, CP [51]			
RAB14 RAB14, member RAS oncogene family (rab-14)	D	C. elegans 1 Human 1		(D) **BP** Brain [7]	(D) **Antidepressants** Blood [29]		(I) **Depression** AMY [44]		9	
SYT1 synaptotagmin I (snt-1)	D	C. elegans 1 Human 1	Linkage [50]	(D) **Stimulants** NAC [52] **BP** Brain [7] OrbitoFC [53]			(I) **Depression** HIP [44] **Stimulants** CP [51] (D) **DBP ST Mice** AMY, PFC [11] **DBP Mice** DHA AMY [12]		9	Distant output
SYT2 synaptotagmin II (snt-1)	D	C. elegans 1 Human 1	Linkage [40] [36]	(D) **Mood Stabilizers** parietal cortex [54] (I) **MDD** DLPFC [55]			(I) **Depression** dentate gyrus [30]		9	
YIPF5 Yip1 domain family, member 5 (F32D8.14)	I	C. elegans 1 Human 1	Linkage [56]	(D) **BP** Brain [7]			(I) **Depression** cingulate cortex [30], [57]		9	Distant output
H3F3A H3 histone, family 3A (his-74)	I	C. elegans 1 Human 1	Linkage [58]	(I) **PTSD** DLPFC BA46 [23]	(I) **Antidepressants** Blood [29]			(I) **DBP Mice** DHA Blood [12]	8.5	
TROVE2 TROVE domain family, member 2 (rop-1)	D	C. elegans 1 Human 2	Linkage [36]		(D) **BP** Lymphocytes [34]		(I) **Depression** AMY [44] **DBP ST Mice** AMY [11] (D) **DBP ST Mice** PFC [11] **Mood Stabilizers** VT [51]	(D) **DBP Mice** DHA Blood [12]	8.5	

ANK2 ankyrin 2, neuronal (unc-44)	D	C. elegans 1 Human 1		(D) **MDD** AMY and cingulate cortex [27] (I) **BP** Brain [7]			(I) **DBP ST Mice** PFC [11]		8	
CLASP2 cytoplasmic linker associated protein 2 (cls-2)	D	C. elegans 1 Human 1		(D) **BP** Brain [7]			(I) **Depression** AMY [44] **DBP NST Mice** PFC AMY [11]		8	
DDO D-aspartate oxidase (daao-1)	I	C. elegans 2 Human 1	Linkage [59 60]	**BP** ACC (BA 24) [61]					8	Distant Output
NAV2 neuron navigator 2 (unc-53)	D	C. elegans 1 Human 1	**BP** [62 63]	(I) **MDD** AMY [64] (D) **BP** PFC BA46/10) [65]					8	
PEBP1 phosphatidyl ethanolamin e binding protein 1 (F40A3.3)	I	C. elegans 1 Human 1	Linkage [66]	(I) **MDD** DLPFC [33]				(D) **Mood Stabilizers** Lymphocyte s [51] **DBP NST Mice** [11] (I) **DBP Mice** DHA Blood [12]	8	
PLA2G6 phospholipas e A2, group VI (cytosolic, calcium-independent) (F45E10.1)	D	C. elegans 1 Human 1	**BP** [67]	(I) **MDD** DLPFC [33]					8	
SYNE1 spectrin repeat containing, nuclear envelope 1 (anc-1)	D	C. elegans 1 Human 1	**BP** [68 3 69 70 6 3 71]		(D) **BP** Blood [34]		(I) **Depression** AMY [44] Medial PFC [72] (D) **Mood Stabilizers**		8	Distant output

							CP [51]			
COX5A cytochrome c oxidase subunit Va (cco-2)	I	C. elegans 1 Human 1		(D) **BP** Brain [7]			(I) **Mood Stabilizers** FC [73]	**DBP Mice** (D) DHA Blood [12]	7.5	
ACADSB acyl-CoA dehydrogenase, short/branched chain (acdh-1)	I	C. elegans 1 Human 1	Linkage [43]	(D) **BP** Brain [7]					7	
EPHX1 epoxide hydrolase 1, microsomal (xenobiotic) (C55B7.4)	I	C. elegans 1 Human 1	Linkage [58] [74]	**BP** ACC (BA 24) [61]					7	Distant output
JPH1 junctophilin 1 (jph-1)	D	C. elegans 1 Human 1	Linkage [37]	(D) **BP** Brain [7]					7	
KAT2B K(lysine) acetyltransferase 2B (pcaf-1)	I	C. elegans 1 Human 1	Linkage [75] **PTSD** [76]		(D) **BP** Blood [15]			(D) **DBP ST Mice** Blood [11]	7	Immediate Input
MSH2 mutS homolog 2 (msh-2)	I	C. elegans 1 Human 1	Linkage [77]	(D) **BP** Brain [7] (I) **MDD** PFC [78]					7	
MSRA methionine sulfoxide reductase A (msra-1)	I	C. elegans 1 Human 1	Linkage [59]	(D) **Depression** FPC [28]					7	
MYH3 myosin, heavy chain 3, skeletal muscle, embryonic (myo-3)	D	C. elegans 1 Human 1	Linkage [50] [79]	(D) **MDD** Choroid plexus [14]					7	
POLH polymerase (DNA directed), eta (polh-1)	I	C. elegans 1 Human 2		(D) **BP** CA1-Stratum oriens [80]	(I) **Mood Stabilizers** Human astrocyte-derived cells (U-87 MG) [81]				7	

PTPN3 protein tyrosine phosphatase, non-receptor type 3 (ptp-1)	D	C. elegans 1 Human 1	Linkage [82]	(D) **BP** Brain [7]					7	
SLC35B3 solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B3 (pst-2)	I	C. elegans 1 Human 1	Linkage [83]	(I) **BP** Brain [7]					7	Distant Output
SLC26A2 solute carrier family 26 (anion exchanger), member 2 (sulp-4)	D	C. elegans 1 Human 1	Linkage [66]	(D) **MDD** AMY and cingulate cortex (D) [27]					7	
CYB5B cytochrome b5 type B (outer mitochondrial membrane) (cytb-5.1)	I	C. elegans 1 Human 1		(D) **BP** Brain [7]					6	
CYP2J2 cytochrome P450, family 2, subfamily J, polypeptide 2 (cyp-33C6)	I	C. elegans 1 Human 2	Linkage [50] [84] [43]		(I) **Relaxation Response** PBMC [20]				6	
FAM184A family with sequence similarity 184, member A (tag-278)	D	C. elegans 1 Human 1	**BP** [63]		(D) **BP** Blood[34]				6	
FBN1 fibrillin 1 (mua-3)	D	C. elegans 1 Human 1	**BP** [85]				(D) **ASD** Postpartum Brain [86]		6	Distant output
GLDC glycine dehydrogenase (decarboxylating)	I	C. elegans 1 Human 1		(I) **BP** PFC (BA46) [87]					6	Distant output

(R12C12.1)										
GPX4 glutathione peroxidase 4 (gpx-7)	I	C. elegans 1 Human 1		(D) **BP** FC [88] HIP [89]					6	
NUAK1 NUAK family, SNF1-like kinase, 1 (unc-82)	D	C. elegans 1 Human 1		(I) **MDD** BA11 [90]					6	
PSENEN presenilin enhancer gamma secretase subunit (pen-2)	I	C. elegans 1 Human 4	Linkage [36]						6	
SMYD3 SET and MYND domain containing 3 (set-18)	D	C. elegans 1 Human 1	**Stimulants** [91]	(D) **BP** Brain [7]					6	
SCD5 stearoyl-CoA desaturase 5 (fat-6)	I	C. elegans 1 Human 1	Linkage [26]				(D) **DBP ST Mice** PFC[11] (I) **DBP Mice** DHA PFC [12]	(D) **DBP Mice** DHA Blood[12]	5.5	
ABCC1 ATP-binding cassette, sub-family C (CFTR/MRP), member 1 (mrp-2)	D	C. elegans 1 Human 1	Linkage [45] [92, 93]		(D) **Chronic Stress** Blood [24]				5	
APMAP adipocyte plasma membrane associated protein (F57C2.5)	I	C. elegans 1 Human 1	Linkage [94] [47]		(D) **Chronic Stress** Blood [24]				5	
CBS cystathionine-beta-synthase (cysl-3)	I	C. elegans 1 Human 1	Linkage [94]		(I) **PTSD** PBMC [95]				5	Distant Output
CTH cystathionase (cystathionine gamma-	D	C. elegans 1 Human 1	Linkage [18] [84, 96]				(I) **Depression** cingulate cortex [30]		5	

lyase) (cth-1)										
CYB5R3 cytochrome b5 reductase 3 (hpo-19)	I	C. elegans 1 Human 1			(D) **Antidepressants** MNC [29]		(D) **DBP ST Mice** PFC [11]		5	
CYP2C18 cytochrome P450, family 2, subfamily C, polypeptide 18 (cyp-33C6)	I	C. elegans 1 Human 1	Linkage [36 77]				(I) **Chronic Stress** AMY [44]		5	
CYP2C9 cytochrome P450, family 2, subfamily C, polypeptide 9 (cyp-33C6)	I	C. elegans 1 Human 1	Linkage [36 77]		(D) **BP** Blood [34] (I) **BP** Blood [34]				5	
MFSD12 major facilitator superfamily domain containing 12 (F16H11.1)	D	C. elegans 1 Human 1	Linkage [97]		(I) **BP** Blood [15]				5	
MON1B MON1 secretory trafficking family member B (sand-1)	I	C. elegans 1 Human 1	Linkage [98]				(I) **Depression** AMY [44]		5	
MYH13 myosin, heavy chain 13, skeletal muscle (myo-3)	D	C. elegans 1 Human 1	Linkage [50 79]		(I) **BP** PBMC [48]				5	
NLGN2 neuroligin 2 (nlg-1)	D	C. elegans 1 Human 1			(D) **Mood Stabilizers** NT2.D1 cells [99]		(I) **DBP Mice** PFC [11] (D) **Mood Stabilizers** AMY [49]		5	
OSTM1 osteopetrosis associated transmembrane protein 1 (F42A8.3)	I	C. elegans 1 Human 1	Linkage [59 60]		(D) **Chronic Stress** Blood [24]				5	

PGM1 phosphoglucomutase 1 (R05F9.6)	I	C. elegans 1 Human 1	Linkage [18]				(D) **Depression** AMY[30]		5	
PIWIL4 piwi-like RNA-mediated gene silencing 4 (prg-2)	I	C. elegans 1 Human 1	Linkage [84]		(D) **BP** Blood [34]				5	
PLEKHH2 pleckstrin homology domain containing, family H (with MyTH4 domain) member 2 (max-1)	D	C. elegans 1 Human 1	Linkage [77]				(I) **Depression** AMY [44]		5	
TRAPPC10 trafficking protein particle complex 10 (Y71G12A.2)	I	C. elegans 1 Human 1	Linkage [100]		(D) **BP** Blood [15]				5	
UFM1 ubiquitin-fold modifier 1 (tag-277)	I	C. elegans 1 Human 1	Linkage [101 93]				(D) **Depression** AMY[44]		5	

Table S3. Top candidate genes for mood and stress-modulated longevity with other evidence for involvement in Longevity (same direction of change), as well as in Aging, Alzheimer Disease, and Suicide (opposite direction of change) (n=30 out of 67 with CFG≥5).

Gene Symbol/Gene Name	Direction of Change In Mianserin C. elegans	Score	Prioritization Total CFG Score	Human Genetic evidence	Human Brain expression evidence	Human Peripheral expression evidence		Nonhuman Brain expression evidence	Nonhuman Peripheral expression evidence	Nonhuman Genetic evidence	CFG Score for Aging, Longevity and Suicide
ANK3 ankyrin 3, node of Ranvier (ankyrin G)	D	C. elegans 1 Human 1	13	**Longevity** [102]		(I) **Suicide** Blood [103]					**4**
COX6A1 cytochrome c oxidase subunit VIa polypeptide 1	I	C. elegans 1 Human 1	**10.5**			(D) **Alzheimer's Disease** Blood mononuclear cell (BMC) [104]					**2**
SOD2 superoxide dismutase 2, mitochondrial	I	C. elegans 1 Human 1	10.5	**Longevity** [105-107] **Aging** [105]	(D) **Suicide** FPC [28]				(D) **Aging** [108] **SOD Deficient Mice**[1] [09]	**Longevity** [110]	**8**
DUS4L dihydrouridine synthase 4-like (S. cerevisiae)	I	C. elegans 1 Human 1	10			(D) **Suicide** Blood [103]					**2**
NEDD4L neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	D	C. elegans 1 Human 1	10			(I) **Suicide** Blood [103]					**2**
MYH11 myosin, heavy chain 11, smooth muscle	D	C. elegans 1 Human 1	9			(I) **Suicide** Blood [103]					**2**
NAV3 neuron navigator 3	D	C. elegans 1 Human 1	9			(I) **Suicide** Blood [103]					**2**

SYT2 synaptotagmin II	D	C. elegans 1 Human 1	9	**Longevity** [102]							**2**
YIPF5 Yip1 domain family, member 5	I	C. elegans 1 Human 1	9			(D) **Suicide** Blood [103]					**2**
TROVE2 TROVE domain family, member 2	D	C. elegans 1 Human 2	8.5			(I) **Suicide** Blood [103]					**2**
ANK2 ankyrin 2, neuronal	D	C. elegans 1 Human 1	8	**Longevity** [102]							**2**
CLASP2 cytoplasmic linker associated protein 2	D	C. elegans 1 Human 1	8			(I) **Suicide** Blood [103]					**2**
DDO D-aspartate oxidase	I	C. elegans 2 Human 1	8		(D) **Suicide** HIP [111]						**4**
NAV2 neuron navigator 2	D	C. elegans 1 Human 1	8	**Longevity** [105]							**2**
PEBP1 phosphatidylethanolamine binding protein 1	I	C. elegans 1 Human 1	8						(D) **Aging** C. elegans [112]		**1**
EPHX1 epoxide hydrolase 1, microsomal (xenobiotic)	I	C. elegans 1 Human 1	7		(D) **Suicide** PFC BA46/10 [113]	(D) **Suicide** Blood [114]					**6**
KAT2B K(lysine) acetyltransferase 2B	I	C. elegans 1 Human 1	7	**Longevity** [107]	(D) **Alzheimer's Disease** HIP [115]						**6**
MSH2 mutS homolog 2	I	C. elegans 1 Human 1	7			(D) **Suicide** Blood [103]					**2**
MSRA methionine sulfoxide reductase A	I	C. elegans 1 Human 1	7	**Aging** [116] [117]	(D) **Suicide** PFC [28]				(D) **Aging** [118]		**7**
POLH polymerase	I	C. elegans	7			(D) **Suicide**					**2**

(DNA directed), eta		1 Human 2				Blood [103]					
PTPN3 protein tyrosine phosphatase, non-receptor type 3	D	C. elegans 1 Human 1	7		(I) **Suicide** Brain [119]						**4**
FAM184A family with sequence similarity 184, member A	D	C. elegans 1 Human 1	6			(I) **Suicide** Blood [103]					**2**
FBN1 fibrillin 1	D	C. elegans 1 Human 1	6		(I) **Suicide** ACC [120]						**4**
GPX4 glutathione peroxidase 4	I	C. elegans 1 Human 1	6	**Aging** [116]						**Aging** [121] [122]	3
NUAK1 NUAK family, SNF1-like kinase, 1	D	C. elegans 1 Human 1	6		(I) **Suicide** BA11 [90]						**4**
CBS cystathionine-beta-synthase	I	C. elegans 1 Human 1	5			(D) **Suicide** Blood [103]					**2**
CTH cystathionase (cystathionine gamma-lyase)	D	C. elegans 1 Human 1	5						(I) **Aging** C. elegans [112]		**1**
CYB5R3 cytochrome b5 reductase 3	I	C. elegans 1 Human 1	5			(D) **Suicide** Blood [103] **Alzheimer's Disease** Blood mononuclear cell (BMC) [104]					**2**
CYP2C9 cytochrome P450, family 2, subfamily C, polypeptide 9	I	C. elegans 1 Human 1	5			(D) **Suicide** Blood [103]					**2**
NLGN2 neuroligin 2	D	C. elegans 1 Human 1	5			(I) **Suicide** Blood [103]					**2**

Table S4 Top candidate genes for longevity with drugs that modulate them (in the same direction) (n= 17 out of 67 with CFG≥5). Underlined may serve as pharmacogenomics blood biomarkers of response to treatment with DHA.

Gene symbol/ Gene Name	Direction of change in Mianserin C.elegans	Modulated by Omega-3	Modulated by Lithium	Modulated by Valproate	Other Drugs	Prioritization Total CFG Score
ANK3 ankyrin 3, node of Ranvier (ankyrin G)	D	(D) **DBP Mice DHA** AMY[12]				13
MYH9 myosin, heavy chain 9, non-muscle	D	(D) **DBP Mice DHA** Blood [12]				12.5
COX6A1 cytochrome c oxidase subunit VIa polypeptide 1	I	(I) **DBP Mice DHA** Blood [12]	(I) **Mood Stabilizers** Cerebral Cortex [21]			10.5
SOD2 superoxide dismutase 2, mitochondrial	I	(I) **DBP Mice DHA (males)** Blood [12]				10.5
NEDD4L neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	D	(D) **DBP Mice DHA** HIP [12]				10
MYH11 myosin, heavy chain 11, smooth muscle	D		(D) AMY [49]			9
NAV3 neuron navigator 3	D			(D) **Mood Stabilizers** AMY, CP [51]		9
H3F3A H3 histone, family 3A	I	(I) **DBP Mice DHA** Blood [12]				8.5
TROVE2 TROVE domain family, member 2	D	(D) **DBP Mice DHA** Blood [12]		(D) VT [51]		8.5
PEBP1 phosphatidylethanolamine binding protein 1	I	(I) **DBP Mice** DHA Blood [12]				8
PLA2G6 phospholipase A2, group VI (cytosolic, calcium-independent)	D	(D) Human plasma [123]			quinacrine	8
SYNE1 spectrin repeat containing, nuclear envelope 1	D			(D) **Valproate** Caudate putamen [17]		8
SYT1 synaptotagmin I	D	(D) **DBP Mice DHA** AMY [12]		(D) AMY [51]		8
COX5A cytochrome c oxidase subunit Va	I		(I) **Mood Stabilizers** FC [73]			7.5
SCD5	I	(I)				5.5

stearoyl-CoA desaturase 5		**DBP Mice** DHA PFC [12]				
ABCC1 ATP-binding cassette, sub-family C (CFTR/MRP), member 1	D				sulfinpyrazone	5
NLGN2 neuroligin 2	D		(D) Amygdala [49]	(D) NT2.D1 cells [99]		5

Table S5. Pathway Analyses for Involvement in Diseases.

		Ingenuity			GeneGO		
		Diseases and Disorders	**P-Value**	**# Molecules**	**Diseases**	**pValue**	**Ratio**
N= 347 Genes Unique Human Ortholog	1	**Cancer**	1.45E-02 - 2.30E-09	294	Arthrogryposis	3.344E-08	6/13
	2	Organismal Injury and Abnormalities	1.53E-02 - 2.30E-09	296	Mouth Diseases	1.869E-07	119/4588
	3	Gastrointestinal Disease	1.53E-02 - 3.31E-06	212	Mouth Neoplasms	2.222E-07	108/4047
	4	Dermatological Diseases and Conditions	1.53E-02 - 5.90E-06	146	Genital Diseases, Female	2.640E-07	264/12925
	5	Respiratory Disease	1.37E-02 - 1.99E-05	49	Genital Neoplasms, Female	2.917E-07	262/12809
N= 134 Genes that have GWAS evidence	1	**Cancer**	1.20E-02 - 1.03E-06	117	**Brain Diseases**	2.314E-07	43/2804
	2	Dermatological Diseases and Conditions	1.20E-02 - 1.03E-06	66	Arthrogryposis, Distal	4.399E-07	4/10
	3	Organismal Injury and Abnormalities	1.20E-02 - 1.03E-06	118	Mouth Diseases	6.760E-07	58/4588
	4	Reproductive System Disease	1.14E-02 - 4.10E-06	59	Mouth Neoplasms	9.066E-07	53/4047
	5	Gastrointestinal Disease	1.20E-02 - 2.93E-05	89	Head and Neck Neoplasms	9.924E-07	77/7011
N=67 Genes CFG ≥5	1	**Cancer**	1.45E-02 - 7.85E-06	60	**Brain Diseases**	2.032E-10	33/2804
	2	Gastrointestinal Disease	1.24E-02 - 7.85E-06	55	Central Nervous System Diseases	1.034E-09	33/2983
	3	Organismal Injury and Abnormalities	1.45E-02 - 7.85E-06	63	Neuroaxonal Dystrophies	4.645E-07	3/5
	4	Psychological Disorders	1.16E-02 - 2.33E-05	10	Genital Diseases, Female	5.856E-07	68/12925
	5	Neurological Disease	1.43E-02 - 3.26E-05	20	Homocystinuria	9.267E-07	3/6
N=9 Genes CFG ≥10	1	Dermatological Diseases and Conditions	4.92E-02 - 1.92E-05	8	Adams-Oliver Syndrome	7.731E-06	2/7
	2	Psychological Disorders	4.50E-02 - 2.24E-05	5	Brain Diseases	8.839E-06	9/2804
	3	Neurological Disease	4.88E-02 - 1.48E-04	6	Central Nervous System Diseases	1.482E-05	9/2983
	4	Organismal Injury and Abnormalities	4.81E-02 - 2.64E-04	8	Nephritis, Hereditary	6.962E-05	2/20
	5	Renal and Urological Disease	3.52E-02 - 2.64E-04	5	Mitochondrial Diseases	8.296E-05	3/139

Table S6 Top biomarkers chosen for panel. For each of the top 9 biomarkers, the probeset that had the best correlation with aging and was concordant with minaserin-treated C. elegans direction of change in expression was chosen (in bold). 5 out of the 9 top genes had concordant probesets (16 out of 25 probesets, 64%). 4 out of 5 probesets for ANK3 were concordant (80%). The best ANK3 probeset (239726_at) had the best correlation of all the concordant probesets in all the biomarkers.

Gene Symbol	CFG Score	Probeset	Psychiatric Patients Correlation With Age (n=737)	Correlation p-value (two-tailed)	Mianserin C. Elegans Change	Concordant with C. elegans direction
ANK3	**13**	**239726_at**	**0.1**	**0.007**	**D**	**Yes**
ANK3	13	206385_s_at	0.028	0.45	D	Yes
ANK3	13	209442_x_at	0.028	0.443	D	Yes
ANK3	13	238786_at	0.026	0.479	D	Yes
ANK3	13	207950_s_at	-0.018	0.619	D	No
MYH9	12.5	211926_s_at	-0.063	0.088	D	No
COX6A1	10.5	224344_at	0.005	0.882	I	No
COX6A1	10.5	200925_at	0.035	0.339	I	No
PPIF	**10.5**	**201489_at**	**-0.066**	**0.075**	**I**	**Yes**
PPIF	10.5	201490_s_at	-0.039	0.296	I	Yes
SOD2	**10.5**	**215078_at**	**-0.064**	**0.085**	**I**	**Yes**
SOD2	10.5	1566342_at	-0.06	0.103	I	Yes
SOD2	10.5	215223_s_at	-0.056	0.126	I	Yes
SOD2	10.5	221477_s_at	-0.037	0.319	I	Yes
SOD2	10.5	216841_s_at	-0.029	0.43	I	Yes
CDC25B	10	201853_s_at	0.067	0.071	I	No
SRD5A1	10	210959_s_at	0.113	0.002	I	No
SRD5A1	10	204675_at	0.133	0.000293	I	No
SRD5A1	10	211056_s_at	0.202	2.9419E-08	I	No
DUS4L	**10**	**205762_s_at**	**-0.029**	**0.438**	**I**	**Yes**
DUS4L	10	205761_s_at	-0.012	0.74	I	Yes
NEDD4L	**10**	**241396_at**	**0.055**	**0.139**	**D**	**Yes**
NEDD4L	10	212448_at	0.039	0.289	D	Yes
NEDD4L	10	212445_s_at	0.021	0.565	D	Yes
NEDD4L	10	226974_at	-0.03	0.414	D	No

Table S7 Compounds that have similar gene expression profile to our top mood and stress modulated longevity genes. Connectivity Map (cmap) (Broad/MIT)[124] results. Cmap comprises a collection of genome-wide transcriptional expression data from cultured human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of functional connections between drugs, genes and diseases through the transitory feature of common gene-expression changes [124], [125]Score of 1 means maximum similarity. Shown are commonly used medications that are similar to our top 9 longevity genes, i.e. may be tested/ repurposed for effects on longevity.

Similarity with the gene expression signature of our top 9 genes/biomarkers for the effects of mood and stress on longevity

rank	cmap name	dose	cell	score	
1	dicoumarol	12 µM	MCF7	1	anticoagulant
2	diethylstilbestrol	15 µM	MCF7	0.948	synthetic estrogen
3	meglumine	20 µM	MCF7	0.936	antiprotozoal
4	troglitazone	10 µM	PC3	0.933	antidiabetic
5	cyclopentolate	12 µM	MCF7	0.923	muscarinic antagonist
6	mycophenolic acid	12 µM	MCF7	0.912	immunosuppressant
7	irinotecan	100 µM	MCF7	0.905	antineoplastic
8	metanephrine	17 µM	MCF7	0.903	adrenergic metabolite
9	gliquidone	8 µM	PC3	0.902	antidiabetic
10	nifedipine	12 µM	PC3	0.901	calcium channel blocker
11	pioglitazone	10 µM	PC3	0.9	antidiabetic
12	terbutaline	7 µM	PC3	0.899	adrenergic agonist
14	capsaicin	13 µM	MCF7	0.895	spice
17	homochlorcyclizine	*10 µM*	PC3	0.888	antihistamine
19	capsaicin	13 µM	MCF7	0.882	spice
20	piracetam	28 µM	HL60	0.882	nootropic
21	minaprine	11 µM	MCF7	0.877	antidepressant
25	quercetin	12 µM	MCF7	0.865	plant flavonoid
47	rosiglitazone	10 µM	PC3	0.807	antidiabetic
52	ergocalciferol	10 µM	MCF7	0.797	Vitamin D
59	resveratrol	18 µM	MCF7	0.788	plant phytoalexin
69	sirolimus	100 nM	HL60	0.778	immunosuppressant
73	estradiol	10 nM	HL60	0.772	estrogen
81	amoxapine	13 µM	MCF7	0.767	antidepressant

Table S8. "Life Switch"

A. Diagnostics and therapeutics. 22 top candidate genes for the effects of mood and stress on longevity from Table S3, that show opposite direction of change to suicide, constituting in essence a "life switch". We also show from Table S4 which of them are modulated in the direction of longevity by DHA, lithium, valproate. Blue- D (decreased in expression). Red-I (increased in expression).

Gene Symbol/Gene Name	Direction of Change In Mianserin C. elegans	Internal Score	Prioritization Total CFG Score	Human Genetic evidence	Human Brain expression evidence	Human Peripheral expression evidence		Drugs
ANK3 ankyrin 3, node of Ranvier (ankyrin G)	D	C. elegans 1 Human 1	13	**Longevity** [102]		(I) **Suicide** Blood [103]		**Omega-3**
SOD2 superoxide dismutase 2, mitochondrial	I	C. elegans 1 Human 1	10.5	**Longevity** [105-107] **Aging**[105]	(D) **Suicide** Brain [28]			**Omega-3**
DUS4L dihydrouridine synthase 4-like (S. cerevisiae)	I	C. elegans 1 Human 1	10			(D) **Suicide** Blood [103]		
NEDD4L neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	D	C. elegans 1 Human 1	10			(I) **Suicide** Blood [103]		**Omega-3**
MYH11 myosin, heavy chain 11, smooth muscle	D	C. elegans 1 Human 1	9			(I) **Suicide** Blood [103]		**Lithium**
NAV3 neuron navigator 3	D	C. elegans 1 Human 1	9			(I) **Suicide** Blood [103]		**Valproate**
YIPF5 Yip1 domain family, member 5	I	C. elegans 1 Human 1	9			(D) **Suicide** Blood [103]		
TROVE2 TROVE domain family, member 2	D	C. elegans 1 Human 2	8.5			(I) **Suicide** Blood [103]		**Omega-3**
CLASP2 cytoplasmic linker associated protein 2	D	C. elegans 1 Human 1	8			(I) **Suicide** Blood [103]		

DDO D-aspartate oxidase	I	C. elegans 2 Human 1	8		(D) **Suicide** Brain [111]			
EPHX1 epoxide hydrolase 1, microsomal (xenobiotic)	I	C. elegans 1 Human 1	7		(D) **Suicide** Brain [113]	(D) **Suicide** Blood [114]		
MSH2 mutS homolog 2	I	C. elegans 1 Human 1	7			(D) **Suicide** Blood [103]		
MSRA methionine sulfoxide reductase A	I	C. elegans 1 Human 1	7	**Aging**[116 117]	(D) **Suicide** Brain [28]			
POLH polymerase (DNA directed), eta	I	C. elegans 1 Human 2	7			(D) **Suicide** Blood [103]		
PTPN3 protein tyrosine phosphatase, non-receptor type 3	D	C. elegans 1 Human 1	7		(I) **Suicide** Brain[119]			
FAM184A family with sequence similarity 184, member A	D	C. elegans 1 Human 1	6			(I) **Suicide** Blood [103]		
FBN1 fibrillin 1	D	C. elegans 1 Human 1	6		(I) **Suicide** Brain [120]			
NUAK1 NUAK family, SNF1-like kinase, 1	D	C. elegans 1 Human 1	6		(I) **Suicide** Brain[90]			
CBS cystathionine-beta-synthase	I	C. elegans 1 Human 1	5			(D) **Suicide** Blood [103]		
CYB5R3 cytochrome b5 reductase 3	I	C. elegans 1 Human 1	5			(D) **Suicide** Blood [103] (D) **Alzheimer's Disease** Blood [104]		
CYP2C9 cytochrome P450, family 2, subfamily C, polypeptide 9	I	C. elegans 1 Human 1	5			(D) **Suicide** Blood [103]		
NLGN2 neuroligin 2	D	C. elegans 1 Human 1	5			(I) **Suicide** Blood [103]		**Omega-3**

B. <u>Other Therapeutics</u>- Compounds that induce a similar gene expression profile to the genes in the Life Switch. Shown are compounds that have gene expression effects similar to the gene expression signature of our top 22 "" life switch" genes. These compounds may be tested/ repurposed for effects on promoting longevity and preventing suicide. (Connectivity Map (cmap) (Broad/MIT)[124] results. Cmap comprises a collection of genome-wide transcriptional expression data from cultured human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of functional connections between drugs, genes and diseases through the transitory feature of common gene-expression changes [124,125]. Score of 1 means maximum similarity.

Similarity with the gene expression signature of the 22 genes changed in expression in opposite direction in suicide and longevity

rank	cmap name	dose	cell	score	
1	GW-8510	10 µM	PC3	1	antineoplastic
2	estradiol	10 nM	PC3	0.963	estrogen
3	5109870	25 µM	MCF7	0.945	antineoplastic
4	apigenin	15 µM	PC3	0.909	plant flavonoid
5	tyrphostin AG-825	25 µM	MCF7	0.897	antineoplastic
6	troglitazone	10 µM	PC3	0.891	antidiabetic
7	hecogenin	9 µM	MCF7	0.882	antineoplastic
8	irinotecan	100 µM	MCF7	0.877	antineoplastic
9	esculin	12 µM	MCF7	0.869	plant sugar
10	resveratrol	10 µM	MCF7	0.862	Plant phytoalexin
11	promazine	12 µM	PC3	0.852	antipsychotic
12	luteolin	14 µM	MCF7	0.83	plant flavonoid
14	enilconazole	13 µM	PC3	0.825	fungicide
15	0175029-0000	10 µM	PC3	0.824	antineoplastic
16	mometasone	8 µM	PC3	0.818	steroid
17	rosiglitazone	10 µM	PC3	0.816	antidiabetic
18	glibenclamide	8 µM	PC3	0.814	antidiabetic
19	menadione	23 µM	PC3	0.804	synthetic vitamin K
20	acacetin	14 µM	PC3	0.801	plant flavonoid
21	folic acid	9 µM	HL60	0.8	vitamin B9

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