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Researchers identify genes linked to the effects of mood and stress on longevity

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The visible impacts of depression and stress that can be seen in a person's face—and contribute to shorter lives—can also be found in alterations in genetic activity, according to newly published research.

In a series of studies involving both *C. elegans* worms and human cohorts, researchers from the Indiana University School of Medicine and

the Scripps Research Institute have identified a series of genes that may modulate the effects of good or bad mood and response to stress on lifespan. In particular, the research pointed to a gene known as ANK3 as playing a key role in affecting longevity. The research was published May 24, 2016 in the Nature Publishing Group journal *Molecular Psychiatry*, the top ranked journal in the field of psychiatry.

"We were looking for genes that might be at the interface between mood, stress and longevity", said Alexander B. Niculescu III, M.D., Ph.D., professor of psychiatry and medical neuroscience at the IU School of Medicine. "We have found a series of genes involved in mood disorders and stress disorders which also seem to be involved in longevity.

"Our subsequent analyses of these genes found that they change in expression with age, and that people subject to significant stress and/or mood disorders, such as people who completed suicide, had a shift in expression levels of these genes that would be associated with premature aging and reduced longevity" said Dr. Niculescu, who is also attending psychiatrist and research and development investigator at the Indianapolis Veterans Affairs Medical Center.

The research began with studies in *C. elegans*, a worm widely used in life sciences research. An earlier study by one of the study co-authors, Michael Petrascheck, Ph.D., of the Scripps Research Institute, found that exposing C. elegans to the antidepressant mianserin, which is used to treat mood and stress disorders, extended the animal's lifespan.

In the *Molecular Psychiatry* study, the researchers methodically conducted a series of analyses to discover, prioritize,

- In *C. elegans*, 231 genes were identified whose activities were altered after administration of mianserin and for which there

were 347 similar genes in humans.

- The 347 human genes were cross-referenced with a genome analysis of data from 3,577 older adults to identify those genes that might be associated with depressive symptoms in humans, resulting in 134 genes that overlapped.
- The 134 genes were prioritized for involvement in mood disorders and stress disorders, using the Niculescu lab's Convergent Functional Genomics approach and comprehensive databases of human and animal model genetic and gene expression studies in psychiatric disorders. The top scoring gene from the list was ANK3, which in recent years has become well known as playing a role in psychiatric disorders.
- Returning to the *C. elegans* model, the researchers tested the effects of mianserin and of oxidative stress on worms with mutated—and therefore inactive—versions of the ANK3 gene, compared to non-mutated wild-type worms. ANK3 expression increases with age in worms. Mianserin maintains lower, youthful levels of ANK3 expression, but does require some ANK3 to be present for its effects on longevity. Thus, there seems to be a "Goldilocks" effect.
- Next, using more than 700 blood samples from patients diagnosed with psychiatric disorders, as well as studying samples from the Marion County (Indianapolis, Ind.) Coroner's office of people who had committed suicide, the investigators found significantly higher levels of expression of ANK3 in older (middle aged) patients than in younger patients, and a shift towards higher ANK3 levels in those who had committed suicide. Higher levels of ANK3 have also been reported independently by others in individuals with Hutchinson-Gilford progeria syndrome, a form of accelerated aging.
- Adding genes that had scored nearly as high as ANK3 in the Convergent Functional Genomics analysis to create a panel of biomarkers showed similar but somewhat stronger results,

particularly among those who had committed suicide.

- Mitochondrial dysfunction was the top biological pathway where the top candidate genes for mood and stress-modulated longevity mapped. Over the last decade, accumulating evidence has suggested a causative link between mitochondrial dysfunction and aging.
- A few of the genes identified in this study are changed in opposite direction in longevity compared to previous reports in Alzheimer's disease, raising the possibility that the treatment of mood and stress disorders earlier in life might have an impact on later life Alzheimer's disease.
- A large number of top genes identified in this study were changed in opposite direction in longevity compared to patterns of expression in suicide revealed by previous studies from the Niculescu group, suggesting the possibility of an evolutionary organismal "life switch", actively controlled by mood and stress.
- Bioinformatics drug repurposing analyses revealed a series of compounds that may act on these genes and promote longevity, such as the relatively innocuous omega-3 fatty acid DHA (docosahexaenoic acid), piracetam, quercetin, vitamin D and resveratrol, along with a series of existing drugs, such as estrogen-like compounds, antidiabetics and rapamycin.

The authors said that "these studies uncover ANK3 and other genes in our dataset as biological links between mood, stress and lifespan, that may be biomarkers for biological age as well as targets for personalized preventive or therapeutic interventions."

Provided by Indiana University

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