Our Ancestors’ Ghosts: Ancestral Exposure to Stress Epigenetically Programs Preterm Birth Risk and Health Outcomes

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Severe distress accelerates aging

The findings by U.S. researchers are the first to link psychological stress directly to biological age

BY BENEDICT CAREY

Some stressful events seem to turn a person's hair grey overnight. Now a team of researchers has found that severe emotional distress—like that caused by divorce, the loss of a job, or caring for an ill child or parent—may speed up the biological aging process by years.

The team's work, which may help explain why divorce and other major life changes have been linked to increased mortality, was published in the June 9 issue of the Proceedings of the National Academy of Sciences.

The researchers studied a group of 5,000 women who had been part of a long-term study of cardiovascular health. They measured the women's stress levels using a standardized questionnaire and then followed them for an average of 12 years. The women who had the highest levels of psychological distress were more likely to develop heart disease and diabetes.

The researchers then looked at how the stress affected the women's telomeres, the ends of their chromosomes that protect the genetic material in the cell. When the telomeres get too short, the cells are more likely to develop cancer.

The findings suggest that psychological stress can lead to the premature aging of cells and, over time, to the development of serious health problems.

Stress and depression are major causes of premature births

Stress and depression in pregnancy are major causes of premature births, experts warn.

Research shows that stress hormones—which play a crucial role in the development of the unborn baby—can disrupt the normal functioning of the placenta, increasing the risk of premature birth.

According to the researchers, stress hormones can cause the placenta to release substances that can damage the blood vessels and cause the placenta to detach from the uterus, leading to early labor.

Premature births are associated with an increased risk of complications for both the mother and the baby, including low birth weight, respiratory problems, and brain damage.

The researchers advise pregnant women to manage stress through techniques such as deep breathing, meditation, and exercise to reduce the risk of premature birth.
Programming of the Stress Response

- **Severe**
- **Mild-Moderate**
- **No Stress**
Stress generates a footprint that travels from one generation to the next...
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HYPOTHESIS: Ancestral Stress Programs Maternal and Offspring Health Trajectories
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Does Stress Program Maternal and Offspring Health?
Gestational Stress Disrupts Maternal Behaviour

Zucchi et al., PLoS ONE, 2013
Can Stress During Pregnancy Influence Preterm Birth Risk?

No Change in Gestational Length...
> 80 genes involved in neurological diseases and mental illness

Zucchi et al., PLoS ONE, 2014
Gestational Stress Alters Potentially Heritable Epigenetic Markers

Zucchi et al., PLoS ONE, 2013
Can Stress Effects Propagate to the Next Generations?
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Model of Transgenerational Maternal Stress

- Unstressed
- Transgenerational (S, SN, SNN, SNNN)
- Multigenerational (S, SS, SSS, SSSS)

F0

F1

F2

F3

F4
Ancestral Stress Shortens Gestational Length

Yao et al., BMC Medicine, 2014

- **F0 N**: 540 hrs.
- **F0 S**: 539 hrs.
- **F1 SN**: 529 hrs.
- **F1 SS**: 527 hrs.
- **F2 SNN**: 529 hrs.
- **F2 SSN**: 527 hrs.
- **F2 SSS**: 527 hrs.
- **F3**: 527 hrs.
Ancestral Stress Elevates Blood Glucose Levels

Yao et al., BMC Medicine, 2014
Ancestral Stress Regulates the miR-200 Family: Role in Pregnancy Maintenance

Yao et al., BMC Medicine, 2014
miR-200 Family Regulates Genes Involved in Pregnancy Maintenance

Yao et al., BMC Medicine, 2014
Placental microRNA Signatures as Proxies for Brain and Uterine Health

Babenko, Kovalchuk et al., unpublished data
Ancestral Stress Impedes Offspring Development

Yao et al., BMC Medicine, 2014
Ancestral Stress Impedes Offspring Development

Yao et al., BMC Medicine, 2014
Ancestral Stress Alters Behaviour During Vulnerable Periods in Life

Erickson et al., PLOS One, 2014
Remote Ancestral Stress Shifts
Patterns of Complex Diseases

Ambeskovic et al., unpublished data
Can Beneficial Experience Offset Adverse Programming?
Environmental Enrichment Mitigates Adverse Programming by Stress

McCreary, Erickson, et al., unpublished data
Environmental Enrichment Mitigates Adverse Programming by Stress

McCreary, Erickson, et al., unpublished data
Ancestral Stress May Better Prepare Future Generations

Benefits
- Resilience
- Metabolic Preparation
Ancestral Stress Also Bears Health Risks

Benefits
- Resilience
- Metabolic Preparation

Risks
- Cardiovascular
- Metabolic
- Aging
Transgenerational Programming of Maternal and Offspring Health

Benefits
- Resilience
- Metabolic Preparation

Risks
- Cardiovascular
- Metabolic
- Aging

Biomarkers
Transgenerational Programming of Maternal and Offspring Health

Benefits
- Resilience
- Metabolic Preparation

Risks
- Cardiovascular
- Metabolic
- Aging

Predict & Prevent

Biomarkers
Building the Foundation for Healthy Futures

- Ancestral stress is a significant influence on lifetime health trajectories.
- Transgenerational inheritance involves epigenetic mechanisms.
- Transgenerational studies may identify new predictive biomarkers of disease.
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Questions?
Does Stress Induce Genuine Transgenerational Effects?
Programming of the Stress Response

- Great Great Grandmother
- Great Grandmother
- Grandmother
- Mother
- YOU!
Proposed mechanisms of action of miR200, ZEB1,2 and STAT5b - Carole Mendelson Lab.

*Williams et al., PNAS, 2012; 109:7529-34*
Transgenerational Epigenetic (microRNA) Programming of Cortical Development

Babenko, Kovalchuk, et al., unpublished data
Down-Stream Metabolic Signatures of Stress

Example: F3-SNN

Kiss, Montina, et al., unpublished
Metabolic Signatures of Age-related Diseases in Hair

Ambeskovic et al., 2013
HYPOTHESIS: Ancestral Stress Programs Maternal and Offspring Health Trajectories