EXPRESSION-BASED POLYGENIC SCORE: A NOVEL METHOD FOR TRANSLATING GENETIC VARIATION INTO BIOLOGICAL FUNCTION

Demonstrated through the HPA axis to reveal how genetic regulation of stress pathways interacts with attachment-based resilience

Peleg Manulis pelegmanulis@gmail.com

BACKGROUND

Decades of behavioral genetic research, summarizing thousands of twin, family, and molecular studies, show that roughly half of our psychological makeup is embedded in our genes. Yet the field has struggled to translate this genetic influence into biologically meaningful models. Earlier studies focused on a few specific genetic variants that were chosen based on theory, producing clear hypotheses but very small and inconsistent effects. Later, genome-wide studies examined millions of variants without theoretical guidance, relying on strict statistical thresholds that often missed biologically important signals. To bridge this gap, we developed the expression-based Polygenic Score (ePS), a new method that combines information from many genetic variants to estimate how active particular biological systems are in the body. This approach provides a biologically coherent and theoretically grounded way to understand how genetic regulation shapes complex traits. As a proof of concept, we focused on the hypothalamic–pituitary–adrenal (HPA) axis, the central system that regulates stress, to explore how genetic regulation of this system interacts with attachment-based resilience in shaping individual differences in stress adaptation.

METHOD

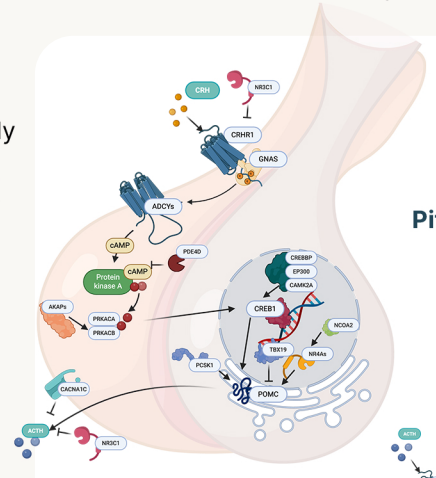
The study included 192 heterosexual Israeli couples (N = 384). Saliva samples were collected using the Oragene OG-600 kit and genotyped with the Illumina GSA-MD-v3 array. Standard quality control was conducted in PLINK. The HPA-axis ePS was calculated by integrating genetic data with expression predictors from the GTEx database, estimating how active genes are likely to be in the anterior pituitary and adrenal glands based on inherited variation. Psychological resilience was defined as the discrepancy between exposure to adverse childhood experiences and current levels of distress, measured with the Global Severity Index from the BSI-18. Attachment to one's best friend, assessed with the ECR-RS, served as a social and emotional moderator of biological resilience.

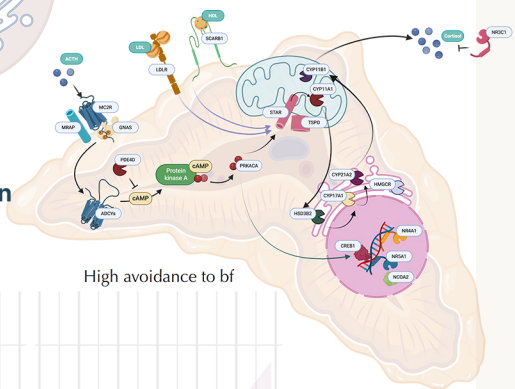
RESULTS

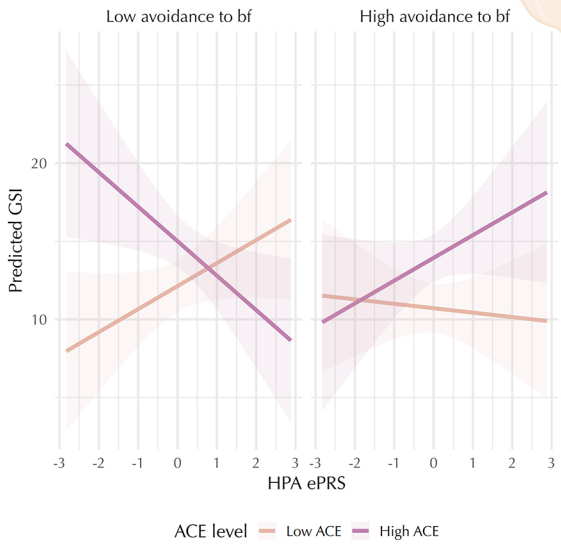
Analyses showed that attachment style shaped the relationship between HPA-axis ePS, early adversity, and stress symptoms. Among securely attached individuals, higher ePS scores, reflecting stronger genetically regulated HPA activity, were associated with lower distress even in the face of high childhood adversity. Among avoidantly attached individuals, the same biological profile predicted greater distress under high adversity. These findings suggest that whether HPA-axis activation is adaptive or harmful depends on the person's attachment orientation.

CONCLUSIONS

This study presents the first development and proof of concept of the ePS framework, introducing a new way to translate genetic information into system-specific measures of biological function. The demonstration using the HPA axis shows how ePS can capture the dynamic interaction between genetic regulation, physiological stress systems, and attachment-based resilience. By combining theoretical insight with comprehensive genetic data, the ePS marks a step forward in behavioral genetics, bridging biology and psychology to deepen our understanding of how genes contribute to human adaptation.







Supervisor - Tsachi Ein Dor