

A TWAS OF OPENNESS TO EXPERIENCE AND CONSCIENTIOUSNESS IMPLICATE NEURONAL SIGNALLING GENES IN THE BASAL GANGLIA IN MATERNAL PERSONALITY

Authors: Geoffrey Chern-Yee Tan^{1,4,5,6,7}, Fong Wei Jing², Maria Paula Leon Mora², Chua Si Ying¹, Tey Kai Ze, Sherwin², Nikita Rane¹, Cheong Zi Gi¹, Jacqueline Chin⁴, Varsha Gupta⁴, Pan Hong⁴, Dennis Wang⁴, Michael J. Meaney^{4,5}

Affiliations of authors: ¹Institute of Mental Health, ²Yale-National University of Singapore, ³National University of Singapore, ⁴Singapore Institute for Clinical Sciences, ⁵Brain-Body Initiative, A*STAR, ⁶Lee Kong Chian School of Medicine, Nanyang Technological University, ⁷Clinical Imaging Research Centre, National University of Singapore

Background: Personality has been shown in other cohorts to have significant genetic loading. It profoundly influences parenting and the attachment style of the child. The Big Five Inventory (BFI) is a multidimensional self-report inventory that identifies the user's position on five scales, namely: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience. Openness to experience observes characteristics of the individual's mental and experiential life including their openness to novel experiences and curiosity. As such, it relates to traits like originality and open-mindedness. Conscientiousness refers to a person's ability to regulate their impulse control in order to engage in goal-directed behaviours. We hypothesized to find genes that are significantly associated with openness to experience and conscientiousness and that genes associated with these traits would show transmission to children.

Methods: From a longitudinal cohort study GUSTO, scores from two of the Big Five Inventory (BFI) personality traits, openness to experience and conscientiousness, were obtained from mothers at postnatal year 4. We first performed LD pruning on the conscientiousness dataset, followed by Principal Component Analysis (PCA), in which PC1-PC4 were extracted for use as covariates in subsequent linear regression style GWAS calculations. TWAS results obtained using PLINK2.0 were used in MetaMany.py to investigate gene-level association with the specific GWAS trait, repeated over multiple brain tissues. Separate Bonferroni correction was done for the various brain tissues, with confidence threshold $\alpha = 0.05$, and genes with a significant p-value after correction were obtained. Secondary analysis was then performed to determine effects on parenting and the traits of their children.

Results: After Bonferroni correction, genes FXYD1 (p-value = 2.66E-06) and SUSD1 (p-value = 1.38E-05) were found to be significantly expressed in nucleus accumbens, part of basal ganglia in the brain, with regards to the conscientiousness personality trait of mothers at postnatal year 4.

After Bonferroni correction, predicted expression of ESPNL in the caudate basal ganglia is positively associated with openness to experience ($R^2 = 0.46$, $F(1,4093) = 2.07$, $p = 1.03e-05$).

Discussion: Both FXYD1 and SUSD1 are neuronal signaling related genes highly expressed in the nucleus accumbens, the neural interface between motivation and action. FXYD1, also known as Domain-Containing Ion Transport Regulator 1, encodes a plasma membrane substrate for several kinases, and is thought to form an ion channel or regulate ion channel activity. SUSD1, also known as sushi domain containing 1, is predicted to enable calcium-binding activity and a integral component of membrane.

While there is no previous literature associating ESPNL gene expression with openness to experience. The caudate is involved in planning movement, learning, memory, reward, motivation, and emotion.

Espin Like (ESPNL) is a protein-coding gene with no previously reported associations with openness to experience or other personality or behavioral traits. Nonetheless, phenotypes associated with this gene involve deafness, autosomal recessive 30, and Autosomal Recessive Nonsyndromic Deafness. As such, ESPNL is involved in pathways related to the sensory processing of sound and olfactory signaling pathways. High expression of ESPNL across several brain tissues further suggests the brain's involvement in ESPNL-associated phenotypes.