A153 · Tryptophan Transporters Modulated by Diet Predict Cognitive and Physical Phenotypes: Implications for Precision Nutrition

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BACKGROUND: Plasma tryptophan is associated with cognitive test scores (semantic fluency, Digit Symbol Substitution Test, Digit Span Forward) and physical function (gait speed, grip strength) in the Long Life Family Study (LLFS). Cognitive and physical performance are only partly genetically inherited, suggesting that gene-dietary interactions influence these outcomes. While enzymes in tryptophan metabolism have been extensively studied, tryptophan transporters, critical regulators of substrate availability, remain understudied.

METHODS: We analyzed data from 4682 LLFS participants with cognitive and physical function, genetic, transcriptomic, metabolomic, and food frequency questionnaire data. We identified tryptophan metabolism pathway components (enzymes from KEGG; transporters validated against peer-reviewed literature) and constructed hierarchical predictive models reflecting known relationships between pathway components. Due to limited samples with complete multi-omics data, we applied forward-backward stepwise selection minimizing Bayesian Information Criteria, requiring final model variables to meet Benjamini Hochberg adjusted significance. Non-significant predictor terms were retained if their interaction term was significant. Models predicted three cognitive test scores and two physical function phenotypes adjusted for age, sex, and education.

RESULTS: SNP-diet and transcript-diet interaction terms were consistently selected as predictors of tryptophan metabolism components, including interactions between SLC3A2 SNP rs2507820 and several measures of amino acid distribution, and conditional amino acid distribution and both SLC3A2 and SLC7A5 transcript expression. These interactions emerged as predictive features in complex multi-omics models.

CONCLUSION: These findings highlight the importance of considering amino acid transporter regulation and dietary composition when modeling the effects of metabolism on phenotypes, and support further investigation into transporter-diet interactions in precision nutrition.