



# Amygdalar Semaphorin signaling integrates emotional, metabolic, and hematopoietic responses

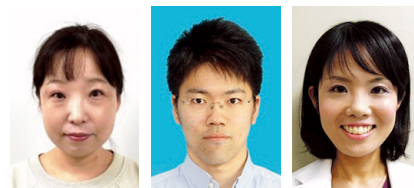
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## Abstract

To identify the central regulatory mechanisms underlying the neuro-immune-metabolic network, we focused on Semaphorin 6D (SEMA6D) expressed in inhibitory neurons of the amygdala. Large-scale human genetic analyses revealed that SEMA6D is associated with both neuropsychiatric traits, such as schizophrenia and ADHD, and metabolic traits, including BMI and body fat mass. SEMA6D-deficient mice exhibited enhanced anxiety-like behavior, resistance to obesity accompanied by sympathetic overactivation, increased peripheral blood cells, and augmented bone marrow hematopoiesis. Spatial transcriptomic analysis further demonstrated that SEMA6D-PLXNA4 signaling in the amygdala contributes to the maintenance of neural circuit integrity and GABAergic signaling.

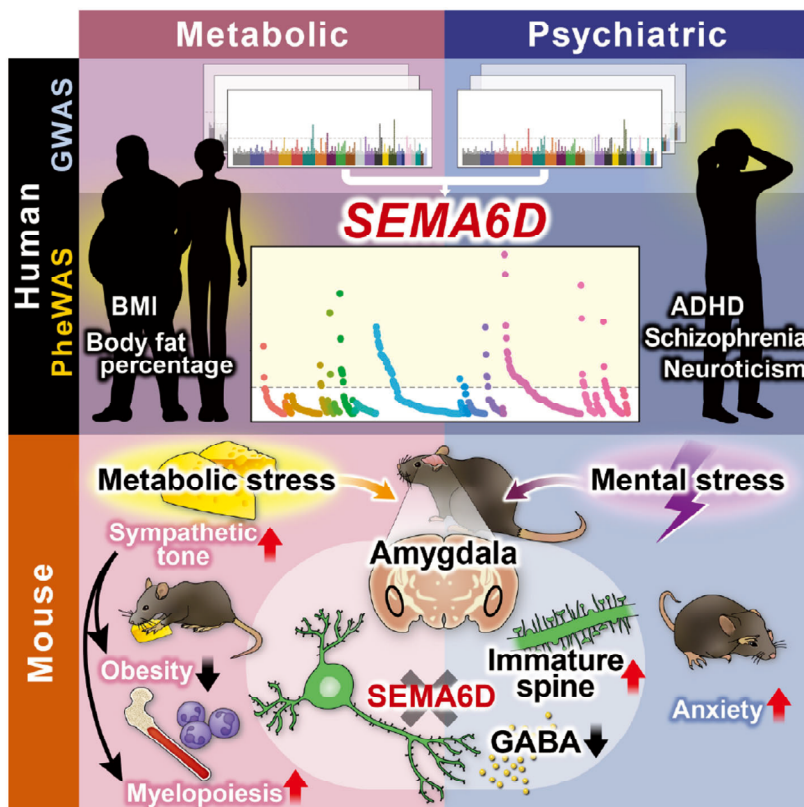
immune-metabolic mechanisms have been studied, their central regulation remains unclear. We identified Semaphorin 6D (SEMA6D) as a key molecule bridging emotional, autonomic, and metabolic control. GWAS revealed SEMA6D as a shared gene between neuropsychiatric and metabolic traits. SEMA6D-deficient mice showed anxiety-like behavior, sympathetic overactivation, and enhanced myelopoiesis, all rescued by  $\beta$ 3-adrenergic blockade. Spatial and single-nucleus transcriptomics showed SEMA6D in CeA inhibitory neurons and its receptor PLXNA4 in BLA excitatory neurons, coordinating GABAergic signaling and emotional-metabolic coupling.

## Significance of the research and Future perspective

This study highlights the significance of the amygdalar SEMA6D-PLXNA4 signaling pathway as a central molecular basis that integrates emotional, metabolic, and hematopoietic responses. This finding provides a brain-centered explanation for the shared mechanisms underlying psychiatric disorders, metabolic abnormalities, and chronic inflammation, and opens new avenues for exploring therapeutic targets through modulation of this neural circuit.

## Background & Results

The nervous, immune, and metabolic systems closely interact to maintain homeostasis, and their disruption leads to neuropsychiatric, metabolic, and inflammatory diseases. While peripheral neuro-



### Patent

### Treatise

### URL

### Keyword

Nakanishi, Yoshimitsu; Izumi, Mayuko; Kang, Sujin; Kumanogoh, Atsushi et al. Semaphorin 6D tunes amygdalar circuits for emotional, metabolic, and inflammatory outputs. *Neuron*. 2024, 112(17), 2955-2972.e9. doi: 10.1016/j.neuron.2024.06.017

Semaphorin, amygdala, anxiety, inflammation, metabolism