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Mini Review

# From Gut–Brain Dysregulation to Immune Hypertension: A FAM120A–FKBP5 Hypothesis

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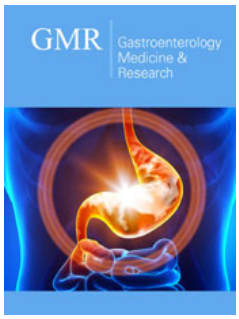


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## Abstract

Irritable Bowel Syndrome (IBS) is a highly prevalent functional gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits, increasingly recognized as a systemic condition involving neuroimmune and endocrine dysregulation. Recent Genome-Wide Association Studies (GWAS) have identified shared genetic susceptibility between IBS and mood disorders, implicating genes involved in neural signaling, stress responses, and immune regulation. Among these, FAM120A has emerged as a potential molecular bridge linking oxidative stress, Src family kinase signaling, and immune homeostasis. This review synthesizes current evidence on the roles of FAM120A, FKBP5, Src kinases, and C-terminal Src Kinase (CSK) in gut–brain interaction, immune signaling, and blood pressure regulation. We propose a unifying hypothesis in which chronic activation of the FAM120A–FKBP5 axis contributes to immune exhaustion, dysregulated T-cell receptor signaling, and inflammation-driven hypertension.

**Keywords**:Irritable bowel syndrome; Gut–brain axis; Protein phosphorylation; FAM120A (OSSA); FKBP5; Src family kinases

## Introduction

Irritable Bowel Syndrome (IBS) is a common disorder of gut–brain interaction affecting populations worldwide, with onset typically occurring in early adulthood. Clinical manifestations include abdominal pain, bloating, and altered bowel habits, with symptom severity fluctuating over time. In severe cases, IBS impairs quality of life to a degree comparable to chronic systemic diseases such as diabetes mellitus or renal impairment. Increasing evidence supports the concept that IBS is not confined to the gastrointestinal tract but reflects broader disturbances involving the nervous, endocrine, and immune systems.

### Genetic overlap between IBS and neuropsychiatric disorders

A landmark genome-wide analysis involving more than 53,000 individuals with IBS identified six susceptibility loci, including NCAM1, CADM2, PHF2/FAM120A, DOCK9, CKAP2/TPTE2P3, and BAG6 [1]. Notably, several of these genes are expressed in the nervous system and have established associations with mood and anxiety disorders. These findings support a shared genetic architecture underlying IBS and psychiatric phenotypes and reinforce the concept of a brain–gut–immune continuum.

### Biological functions of FAM120A

The FAM120A gene encodes the Oxidative Stress–Associated Src Activator (OSSA), a multifunctional RNA-binding protein. FAM120A protects cells from oxidative stress-induced apoptosis by activating Src Family Kinases (SFKs) and by binding specific mRNAs, including IGF2, thereby promoting its extracellular secretion [2]. Beyond its cytoprotective role, FAM120A has been implicated in mTOR signaling, cellular metabolism, and stress-responsive

pathways, positioning it as a key integrator of environmental and intracellular signals.

### Src family kinases and phosphorylation-dependent signaling

Src kinases are non-receptor tyrosine kinases that regulate essential cellular processes such as proliferation, migration, adhesion, and survival. Members of the Src family are activated through phosphorylation events downstream of cell-surface receptors, triggering intracellular signaling cascades that modulate gene expression and immune responses [3,4]. Phosphorylation itself represents a fundamental regulatory mechanism in biology, allowing rapid and reversible control of protein activity and signal amplification in response to extracellular stimuli [5-9].

### CSK, immune regulation, and blood pressure control

C-terminal Src Kinase (CSK) is a critical negative regulator of Src family kinases. Genetic and experimental studies have linked the CSK locus (15q24) to blood pressure regulation across diverse populations. CSK insufficiency induces aldosterone overproduction with zonal specificity in the adrenal glands, leading to increased sodium reabsorption, plasma volume expansion, and hypertension [3]. In the immune system, CSK suppresses T-Cell Receptor (TCR) signaling, thereby preventing excessive T-cell activation and exhaustion [10,11].

### FKBP5 as a stress and immune modulator

FKBP5 is a co-chaperone protein that modulates glucocorticoid receptor sensitivity and plays a pivotal role in stress responsiveness, inflammation, and psychiatric disease susceptibility. Its activity is tightly regulated by phosphorylation and interaction with upstream signaling molecules. Dysregulated FKBP5 expression has been linked to chronic stress states, immune activation, and metabolic disturbances [12].

### A hypothetical FAM120A–FKBP5–CSK pathway in hypertension

Based on available evidence, we propose a hypothesis in which chronic activation of FAM120A leads to sustained stimulation of FKBP5. Over time, this persistent signaling may result in functional exhaustion or depletion of FAM120A, compromising its ability to support CSK activity. Reduced CSK function would, in turn, amplify Src kinase signaling and T-cell receptor activation. The resulting immune dysregulation promotes chronic inflammation, a recognized driver of hypertension development and progression. Failure to restrain TCR signaling may thus represent a mechanistic link between gut–brain dysregulation, immune activation, and elevated blood pressure.

### Clinical and research implications

Understanding the molecular interplay between FAM120A, FKBP5, Src kinases, and CSK may open new avenues for therapeutic intervention in IBS-associated systemic complications, including immune-mediated hypertension. Targeting phosphorylation-dependent signaling pathways or restoring immune checkpoint control could represent novel strategies for preventing inflammation-driven cardiovascular disease in susceptible individuals.

## Conclusion

IBS should be viewed as a systemic disorder with genetic, neuropsychiatric, immune, and cardiovascular dimensions. The proposed FAM120A–FKBP5–CSK axis offers a unifying framework linking gut–brain dysfunction to immune exhaustion and hypertension. Further experimental and clinical studies are required to validate this hypothesis and to explore its translational potential.

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