Neuroinflammation-Related Genes

🧠 Microglial Activation and Immune Regulation

Gene	Function
TREM2	Regulates microglial response to damage; mutations associated with Alzheimer's disease.
CD33	Inhibits microglial phagocytosis; involved in neurodegenerative risk.
CX3CR1	Microglia-neuron communication; modulates neurotoxicity and synaptic pruning.
TLR4	Recognizes damage signals (DAMPs); activates NF-κB inflammatory pathway.
P2RY12	Homeostatic microglial marker; mediates chemotaxis.

🔥 Cytokines and Chemokines

Gene	Function
IL1B	Encodes interleukin-1β; promotes neuroinflammation and fever.
TNF	Tumor necrosis factor-α; central in acute neuroinflammatory response.
IL6	Mediates both pro- and anti-inflammatory effects in the CNS.
CCL2	Monocyte chemoattractant protein-1; attracts macrophages to CNS lesions.
CXCL10	Chemoattracts activated T-cells; elevated in autoimmune encephalitis.

🧪 Oxidative Stress and Blood-Brain Barrier Disruption

Gene	Function
NOX2	Generates ROS; contributes to oxidative neuronal damage.
MMP9	Degrades extracellular matrix; implicated in blood-brain barrier leakage.
AQP4	Water channel protein; involved in brain edema and astrocyte function.

🧬 Neurodegeneration and Clearance

Gene	Function
APP	Amyloid precursor protein; source of Aβ peptides in Alzheimer’s.
PSEN1/2	γ-secretase complex components; mutations lead to abnormal amyloid processing.
ABCA7	Lipid transporter; modulates microglial phagocytosis and cholesterol homeostasis.

📊 Common in Mendelian Randomization Studies

Gene	Function
IL6R	IL-6 receptor; instrumental variable in MR studies of inflammation.
CRP	C-reactive protein gene; systemic inflammation marker.
TREM2	See above; frequently used in genetic studies of microglial response.
MMP9	See above; associated with hemorrhagic transformation.

In a Mendelian Randomization study + in silico gene functional analysis Quanming Zhou et al. from the Department of Neurosurgery, Affiliated Hospital of Putian University, Putian, Fujian, China published in the International Journal of Neuroscience to determine whether neuroinflammation-related genes causally influence intracerebral hemorrhage (ICH) risk using two-sample Mendelian randomization (MR), and to explore underlying mechanisms via protein-protein interaction (PPI), Gene Ontology (GO), and Gene Set Enrichment Analysis (GSEA). Increased expression of **CHUK** and **CTLA4**

genes is causally associated with higher ICH risk in both EBI-ICH and Finn-ICH datasets (e.g., CHUK OR = 1.17–1.25; CTLA4 OR ≈ 1.23–1.29). These associations implicate NF-κB signaling and immune regulation pathways. CHUK and CTLA4 may represent novel therapeutic targets for ICH intervention [1)]

Critical appraisal

Strengths

- **Robust MR design**: Use of two independent GWAS datasets (Ebi, Finn) enhances result validity. - **Consistent findings**: Both datasets showed similar effect sizes for CHUK and CTLA4. - **Functional follow-up**: PPI, GO, and GSEA reinforce biological plausibility, particularly NF-κB and immune pathways.

Limitations

- **SNP significance threshold loosened**: Instrument selection used $p < 5\times10^{-6}$ — more permissive than standard genome-wide ($p < 5\times10^{-8}$), potentially increasing weak instrument bias. - **Population limitation**: Both GWAS datasets are European-only; findings may not generalize to other ancestries. - **Gene expression inference**: MR infers expression effects indirectly—no direct transcriptomic or proteomic validation in brain tissues. - **No experimental validation**: While gene-level associations imply causality, functional studies (e.g. knockdown, inhibition) are necessary to prove therapeutic relevance.

Intellectual rigor

Authors presented sensitivity analyses (MR-Egger, weighted median) and adjusted for pleiotropy. However, quantitative details on IV strength (e.g. F-statistics) and pleiotropy metrics (e.g. MR-PRESSO outputs) are missing in the abstract — these should be transparently reported.

Final verdict: 6.5 / 10

Good MR methodology and replication, biologically plausible pathways, but limited by relaxed instrument selection, lack of diverse populations, and no direct validation in clinical or experimental settings.

Takeaway for practicing neurosurgeons

Genetic upregulation of CHUK and CTLA4 may predispose individuals to ICH via enhanced NF-κB-mediated neuroinflammation. Clinicians should watch for emerging therapies targeting these pathways—as they may offer future risk stratification tools or therapeutic targets.

Bottom line

This MR study identifies CHUK and CTLA4 as potential causal genetic contributors to ICH risk, supporting the role of NF-κB–driven neuroinflammation in hemorrhagic stroke. Confirmatory functional and clinical studies are required before translation.

1)

Zhou Q, Wu S, Kang Y. Causal Associations Between Neuroinflammation-Related Genes and Intracerebral Hemorrhage: An Integrated Study of Mendelian Randomization and Gene Functional Analysis. Int J Neurosci. 2025 Jul 2:1-14. doi: 10.1080/00207454.2025.2529232. Epub ahead of print. PMID: 40601346.