

Literature Validation

Table I Hub genes, enriched pathways, heavy metal associations, and literature validation

Hub Gene	Major Enriched Pathways (KEGG / Biological)	Heavy Metals Implicated	Disease Relevance	Literature Support	References
SNCA	Synaptic signalling, protein aggregation, vesicle trafficking	Pb, Mn, Cd	PD, AD	Experimental and epidemiological studies	(Doroszkiewicz et al., 2023; Tyczyńska et al., 2024)
IL6	Neuroinflammatory signalling, cytokine–cytokine receptor interaction	Pb, Cd	AD, MS, ASD/ADHD	In vivo and population-based studies	(Kim et al., 2022)
TNF	Cytokine signalling, apoptosis, immune response	As, Cd, Hg	ALS, MS, ASD/ADHD	Cell culture and animal models	(Farhana Tasleem et al., 2025; Lin et al., 2022)
CASP3	Apoptosis, mitochondrial dysfunction, cell death pathways	Cd, Hg	ALS, MS	Toxicological and mechanistic studies	(Arruebarrena et al., 2023; Dhilleswara Rao et al., 2024; Yu et al., 2023)
APOE	Lipid metabolism, amyloid processing, synaptic regulation	Pb	AD	Experimental and clinical studies	(Althobaiti, 2025; Islam et al., 2022)

TP53	DNA damage response, apoptosis, oxidative stress regulation	Cd, As, Hg	ALS, AD, MS	Cellular stress and toxicogenomic studies	(Jaishankar et al., 2014; Jomova et al., 2025)
BCL2	Apoptosis regulation, mitochondrial membrane integrity	Cd, Hg	ALS, MS	Experimental apoptosis studies	(Mayer & Oberbauer, 2003)
IFNG	Immune activation, inflammatory signaling, microglial response	Pb, As	MS, ASD/ADHD	Immunological and exposure studies	(Wei et al., 2024)
PTGS2	Prostaglandin synthesis, inflammatory response	Pb, Cd	AD, PD	In vivo neuroinflammation studies	(Choe et al., 2024; Imran et al., 2020)
HMOX 1	Oxidative stress response, heme metabolism, antioxidant defense	As, Cd, Hg	AD, PD, ALS	Oxidative stress and metal toxicity studies	(Elsayed & Foo, 2025; Schipper, 2000)