Do genes associated with Neurodevelopmental and Psychiatric Disorders often involve the Immune System and Mitochondria?

Yes, genes linked to **neurodevelopmental and psychiatric disorders** frequently involve both **immune system** and **mitochondrial** pathways.

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The evidence supporting this convergence comes from genome-wide association studies, transcriptomic analyses, and multi-omics investigations across multiple disorders.

Shared Genetic Architecture Between Immune and Neurodevelopmental Disorders

Genome-wide analyses reveal significant genetic correlations between neurodevelopmental disorders and immune disorders, with 50–90% of immune disorder genetic variants shared with neurodevelopmental disorders (Xiu et al., 2024). A cross-trait GWAS meta-analysis identified 154 genome-wide significant loci, including 8 novel pleiotropic loci, with pathway analysis implicating neural signaling, inflammatory response, and PI3K-Akt signaling as shared pathways (Xiu et al., 2024). Linkage disequilibrium score regression across eight psychiatric disorders confirmed significant genetic correlations with multiple immune-related phenotypes, including autoimmune conditions such as Crohn's disease, lupus, and ulcerative colitis (Tylee et al., 2018).

Disorder	Immune Gene Evidence	Key Immune Pathway
ASD	HLA class I/II alleles, interferon-α signaling	Cytokine production, TLR signaling (Gevezova et al., 2023; Nudel et al., 2019)
Schizophrenia	C4 complement locus, HLA genes	Innate immunity, neuroinflammation (Nudel et al., 2019)
ADHD	HLA-DRB1 DR4, shared immune variants	Inflammatory mediator signaling (Nudel et al., 2019; Xiu et al., 2024)

FIGURE 1 Immune gene evidence and pathways across major neurodevelopmental disorders

HLA genes, which encode proteins central to immune regulation, show reproducible associations with autism and intellectual disability in a Danish sample of over 65,000 individuals (Nudel et al., 2019). A multivariate Genomic SEM analysis across 11 immune-mediated diseases and 13 psychiatric disorders identified six significant factor correlations, indicating that pairwise genetic associations often reflect broader risk-sharing across clusters rather than disorder-specific effects (Breunig et al., 2024).

Mitochondrial Gene Involvement in Psychiatric Disorders

Nuclear-encoded mitochondrial gene variants show significant association with bipolar disorder and schizophrenia, with mitochondrial polygenic risk scores explaining approximately 3% of phenotypic variance in each (Choi et al., 2024). Mendelian randomization across seven mental disorders identified mitochondria-related genes with multi-omics evidence, including RMDN1 for ADHD and ACADVL, ETFA, MMAB, and PPA2 for schizophrenia (Lu et al., 2025). Mitochondrial DNA copy number shares significant global-level genetic overlap with all five major psychiatric disorders tested — ADHD, ASD, bipolar disorder, major depression, and schizophrenia — with functional enrichment highlighting neurodevelopmental pathways (Xue et al., 2026).

- **Copy number variants** in neurodevelopmental disorders show mitochondrial gene enrichment comparable to synaptic gene enrichment, with interaction networks converging on mitochondrial translation (Robinette et al., 2026).
- The 3q29 and 22q11.2 deletions, both high-risk CNVs for ASD and schizophrenia, produce convergent dysregulation of mitochondrial ribosome and translation machinery in cortical organoids (Robinette et al., 2026).
- Mitochondria-related gene signatures in major depressive disorder show intimate association with immune cell infiltration patterns (Liu et al., 2024).

The brain's disproportionate energy demand — consuming 20% of oxygen and 25% of glucose despite representing 2–3% of body mass — makes partial mitochondrial defects sufficient to predispose to neuropsychiatric disorders from autism to Alzheimer's disease (Pei & Wallace, 2017).

Immune–Mitochondrial Crosstalk in Neurodevelopment

Inflammatory mediators from activated microglia and infiltrating immune cells alter mitochondrial function, creating a feedforward loop linking neuroinflammation to mitochondrial dysfunction and neurodegeneration (Gevezova et al., 2023). In ASD, upregulated peripheral immune-inflammatory pathways — including interferon-α signaling and Toll-like receptor signaling — may drive CNS neuroinflammation and downstream mitochondrial electron transport chain dysfunction, ultimately disrupting transsynaptic transmission and neurodevelopment (Gevezova et al., 2023).

Maternal immune activation during gestation elevates inflammatory mediators that disrupt fetal neurodevelopment through microglial hyperactivation, aberrant synaptic pruning, oxidative stress, and mitochondrial dysfunction (Yong et al., 2025). Transcriptomic annotation of shared connectivity patterns across ASD, ADHD, and schizophrenia revealed that transdiagnostic genes are associated with both serotonin transporter and cytochrome c oxidase, while disorder-specific deviations linked to glutamatergic plasticity and immune activation in ASD and broad synaptic plus immune-metabolic dysregulation in schizophrenia (Diao et al., 2026).

In children with paediatric acute-onset neuropsychiatric syndrome, RNA sequencing revealed downregulated mitochondrial activity alongside impaired immune responses, with Toll-like receptor stimulation assays showing reduced TNF and IL-6 production (Han et al., 2025). Cross-disorder transcriptomic analysis of 2,467 postmortem brains found that over 60% of curated immune-related genes showed altered expression in at least one of six brain disorders, with co-expression networks demonstrating that neuroimmune transcripts interact with neuronal systems contributing to pathology (Chen et al., 2022).

Genes encoding proteins with mitochondrial localization are increasingly associated with intellectual disability, epileptic encephalopathy, and autism spectrum disorders, including well-known neurodevelopmental genes not previously suspected of mitochondrial function (Ortiz-González, 2021). The KCTD gene family, implicated in multiple neurodevelopmental and neuropsychiatric disorders, includes members with roles in autophagy-lysosome pathways affecting mitochondria (KCTD7) and nutrient signaling to mTORC1 (KCTD11) (Teng et al., 2019).

Taken together, the evidence across genetic correlation studies, transcriptomic profiling, and mechanistic investigations consistently demonstrates that immune system and mitochondrial pathways represent convergent biological mechanisms in neurodevelopmental and psychiatric disorder risk genes — though the precise causal direction between immune activation and mitochondrial dysfunction remains an active area of investigation.

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