Genomics, the Immune System and Neurodevelopmental and Psychiatric Disorders

Genomics, Immunity, and Brain Disorders: Key Connections

Genomic studies increasingly show that genetic risk for neurodevelopmental and psychiatric disorders is intertwined with variation in the immune system, but the strength and nature of this link differs by disorder and by immune pathway.

Shared Genetic Architecture Between Immune and Psychiatric Traits

- Large GWAS-based correlation studies find **significant genetic sharing** between multiple psychiatric disorders (schizophrenia, bipolar disorder, depression, ADHD, Tourette, OCD, anorexia) and immune-mediated diseases or immune traits (Breunig et al., 2024; Tylee et al., 2018; Grove et al., 2019; Xiu et al., 2024; Chen et al., 2022; O'Dushlaine et al., 2015).
- Using Genomic SEM, immune diseases cluster along an **autoimmune–autoinflammatory continuum**; these immune factors show distinct correlations with psychiatric "internalizing," "psychotic/schizophrenia–bipolar," "compulsive," and "substance use" factors rather than a single uniform link (Breunig et al., 2024; Dardani et al., 2024).
- For neurodevelopmental disorders specifically, 50–90% of variants in immune disorders are shared with them, and 30 pleiotropic loci map to pathways including **inflammatory responses and PI3K–Akt signaling** (Xiu et al., 2024).

Examples of Genomic Links

Relationship	Key finding	Citations
Psychiatric ↔ immune diseases	Multiple significant genome-wide genetic correlations; localized shared loci, especially for schizophrenia with several autoimmune diseases	(Tylee et al., 2018; Breunig et al., 2024; Grove et al., 2019; Chen et al., 2022)
NDDs ↔ immune disorders	High polygenic overlap; 154 shared loci, 8 novel pleiotropic; inflammatory and neural signaling pathways	(Xiu et al., 2024)
HLA region	Specific HLA alleles protect against autism and intellectual disability; supports HLA involvement in neurodevelopment	(Nudel et al., 2019)

FIGURE 1 Illustrative genomic links between immunity and brain disorders

Immune Pathways, Brain Gene Expression, and Development

- Cross-disorder GWAS/meta-analyses identify risk loci enriched in genes expressed in the **developing brain**, with roles in neurodevelopment and sometimes immune regulation (Consortium & Smoller, 2019; Gandal et al., 2018; Grove et al., 2019; Salenius et al., 2024; Wu et al., 2020; Prata et al., 2019).
- Pathway and gene-set analyses highlight **immune and histone pathways**, alongside neuronal signaling and postsynaptic density, as enriched for psychiatric risk variants (Gandal et al., 2018; Chen et al., 2022; Iakunchykova et al., 2024).
- Neuroimmune transcriptome work shows widespread dysregulation of innate immune genes in ASD, schizophrenia, bipolar disorder, depression, Alzheimer's and Parkinson's disease, but common SNPs explain only a minority of these immune-expression changes, suggesting substantial environmental or non-GWAS genetic contributions (Chen et al., 2022).

Causality and Immune Biomarkers

- Mendelian randomization and colocalization analyses across 736 immune-related biomarkers support **potential causal roles** for 29 brain or systemic immune markers in schizophrenia, bipolar disorder, depression and Alzheimer's disease; 20 are druggable targets (e.g., ACE, CD40) (Grove et al., 2019).
- Another MR study finds **no clear causal effect** of three classic autoimmune diseases (SLE, RA, type 1 diabetes) on ADHD, ASD or schizophrenia, but does identify specific pro-inflammatory factors (e.g., cytokine receptors) implicated in these neurodevelopmental disorders (Qin et al., 2025).
- A synthesis of genetic causal-inference work concludes that immune-related genes are overrepresented among GWAS hits for major psychiatric disorders and encourages more refined, pathway-level causal analyses (Iakunchykova et al., 2024).

Conclusion

Genomic data show substantial—but nuanced—overlap between immune-related variation and risk for neurodevelopmental and psychiatric disorders. Shared loci and pathways center on inflammatory and neurodevelopmental signaling, with both brain-specific and systemic immune processes implicated. However, not all autoimmune conditions causally drive these disorders, and much immune dysregulation appears shaped by complex gene–environment interactions rather than simple one-to-one genetic effects.

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