# How could understanding the relationship between In-Born Errors of Immunity and Neurodevelopmental and Psychiatric Disorders radically transform our approaches to Justice-Involved and Homeless populations?

## **Immune-Neuro Genetic Overlap** Could Reshape Justice and Homelessness Policy

Understanding the shared genetic architecture between inborn errors of immunity (IEI) and neurodevelopmental or psychiatric disorders could reframe behavioral and cognitive conditions in justice-involved and homeless populations as potentially rooted in identifiable immune-genetic dysfunction rather than purely psychosocial failure. One-third of IEI-causing genes are also linked to neurodevelopmental disorders, with these shared genes primarily involved in immune development and DNA repair pathways (Serra et al., 2025). IEI-associated genes are expressed in neural lineages during human brain development, and IEI mutations directly impair neurodevelopmental trajectories even in the absence of immunological challenges (Demenego et al., 2025). Approximately 11% of genes known to cause primary immunodeficiency also confer neurological abnormalities ranging from intellectual disability to seizures and motor delay (Roifman & Vong, 2023).

### Genetic and Mechanistic Overlap

| Mechanism | Immune Consequence | Neurological Consequence |
|---|---|---|
| DNA repair defects (e.g., ataxia-telangiectasia) | Immunodeficiency | Cerebellar degeneration, ataxia (Xiao et al., 2025) |
| CXCR4 hyperactivation (WHIM syndrome) | Immunodeficiency | Cerebellar foliation defects, sensorimotor dysfunction (Demenego et al., 2025) |
| Chromatin remodeling defects | Combined immunodeficiency | Autism spectrum disorder, intellectual disability (Xiao et al., 2025) |
| Cytokine signaling dysregulation | Autoinflammation | Encephalopathy, seizures, cognitive decline (Xiao et al., 2025; Yiu et al., 2026) |
| Type I interferonopathy | Immune dysregulation | Neurodevelopmental impacts (Anderson et al., 2025) |

FIGURE 1 Shared mechanisms linking inborn errors of immunity to neurological and neurodevelopmental outcomes

Genetic correlations between neurodevelopmental and immune disorders are significant, with 50–90% of immune disorder genetic variants shared with neurodevelopmental disorders (Xiu et al., 2024). Cross-trait analysis identified 154 genome-wide significant pleiotropic loci, with shared pathways including neural signaling, inflammatory response, and PI3K-Akt signaling (Xiu et al., 2024). IEI mutations cause dysregulated immune activation and chronic inflammation affecting multiple organs, including changes in morphogenesis and plasticity of the central nervous system (Jyonouchi, 2023).

### Population-Level Psychiatric Risk

Primary humoral immunodeficiencies are robustly associated with psychiatric disorders (adjusted OR 1.91) and suicidal behavior (adjusted OR 1.84), with associations remaining significant in sibling comparisons (Isung et al., 2020). Offspring of mothers with primary immunodeficiencies show increased risk of any psychiatric disorder (IRR 1.17) and suicidal behavior (IRR 1.20), with the highest risk when PIDs co-occur with autoimmune diseases (Isung et al., 2023). Childhood maltreatment produces a transdiagnostic increase in pro-inflammatory immune markers among psychiatric patients, with IL-6 identified as a significant mediator between maltreatment exposure and adult psychiatric diagnosis (Van Den Noortgate et al., 2025).

### Implications for Justice-Involved and Homeless Populations

- **Diagnostic reframing**: Neuroinflammation may be the sole or presenting manifestation of an underlying IEI, meaning psychiatric symptoms in underserved populations could reflect undiagnosed immune-genetic disorders rather than primary mental illness (Yiu et al., 2026).
- **Underdiagnosis in marginalized groups**: IEI recognition remains limited globally, and PIDD cohorts in the US overrepresent non-Hispanic White patients, suggesting systemic diagnostic gaps in populations overrepresented in justice and homelessness systems (Brandão et al., 2026; Di Ruffano et al., 2025).
- **Targeted treatment potential**: Early brain-targeted intervention with a CXCR4 antagonist rescued both morphological and behavioral defects in IEI models, demonstrating that neurodevelopmental IEI manifestations can be brain-specific and pharmacologically reversible (Demenego et al., 2025).
- **Immune-based stratification**: Immunogenetic profiling could enable patient stratification into homogeneous subgroups with inflammation-driven psychopathology, supporting personalized therapeutic strategies over one-size-fits-all approaches (Clerc et al., 2026).

The translational importance is substantial: recognizing neurological involvement in IEIs can improve early diagnosis and multidisciplinary care, while deeper understanding of immune-neural crosstalk opens avenues for targeted anti-inflammatory treatments or gene therapies addressing both immune and neural dysfunction (Xiao et al., 2025). For justice-involved and homeless populations—where childhood trauma, chronic inflammation, and undiagnosed neurodevelopmental conditions converge—immunogenetic screening and mechanism-based immune treatments could shift policy from punitive or custodial responses toward precision medical intervention (Pape et al., 2019; Van Den Noortgate et al., 2025).



### References

Anderson, S. R., Jin, R. M., & Molofsky, A. (2025). Neuroimmune mechanisms of neurodevelopmental disorders.. *Biological psychiatry*. https://doi.org/10.1016/j.biopsych.2025.10.023

Brandão, P. S., Conceição, C., & Neves, F. J. (2026). Neuroimaging in inborn errors of immunity: More than infections. *Neuroradiology, 68*, 299 - 326. https://doi.org/10.1007/s00234-025-03895-5

Clerc, L. S., Bernard, J., Choi, J., Andreazza, A., Zagury, J., & Leboyer, M. (2026). Immunogenetic Variants in Major Mental and Neurodevelopmental Disorders.. *Biological psychiatry, 99 11*, 1002-1012. https://doi.org/10.1016/j.biopsych.2026.03.996

Demenego, G., Mancinelli, S., Borreca, A., Proce, R. O., Aragona, V., Miotto, M., Cremonesi, M., Zucchelli, L., Corradini, I., Kim, E., Ilić, K., Fraviga, E., Pellegrino, L., Badolato, R., Rusconi, R., Pozzi, D., Kallikourdis, M., Cash, D., Matteoli, M., & Lodato, S. (2025). Neurodevelopmental origins of structural and psychomotor defects in CXCR4-linked primary immunodeficiency. *Neuron, 113*, 2636 - 2655.e9. https://doi.org/10.1016/j.neuron.2025.05.016

Di Ruffano, L. F., Carr, E., Edwards, M., Arber, M., Grilo, S. A., Posey, J., Abdalgani, M., & Orange, J. (2025). Reported Demographics of Primary Immunodeficiency Diseases in the United States.. *The journal of allergy and clinical immunology. In practice, 13 9*, 2460-2474. https://doi.org/10.1016/j.jaip.2025.06.015

Isung, J., Williams, K., Isomura, K., Gromark, C., Hesselmark, E., Lichtenstein, P., Larsson, H., De La Cruz, L. F., Sidorchuk, A., & Mataix-Cols, D. (2020). Association of Primary Humoral Immunodeficiencies With Psychiatric Disorders and Suicidal Behavior and the Role of Autoimmune Diseases. *JAMA Psychiatry, 77*, 1 - 9. https://doi.org/10.1001/jamapsychiatry.2020.1260

Isung, J., Isomura, K., Williams, K., Zhang, T., Lichtenstein, P., De La Cruz, L. F., Sidorchuk, A., & Mataix-Cols, D. (2023). Association of Primary Immunodeficiencies in Parents With Psychiatric Disorders and Suicidal Behavior in Their Offspring.. *JAMA psychiatry*. https://doi.org/10.1001/jamapsychiatry.2022.4786

Jyonouchi, H. (2023). Inborn errors of immunity present with neuropsychiatric symptoms overlapping with autistic behavioral symptoms. *Journal of Translational Genetics and Genomics*. https://doi.org/10.20517/jtgg.2023.32

Pape, K., Tamouza, R., Leboyer, M., & Zipp, F. (2019). Immunoneuropsychiatry — novel perspectives on brain disorders. *Nature Reviews Neurology, 15*, 317-328. https://doi.org/10.1038/s41582-019-0174-4

Roifman, C., & Vong, L. (2023). Neurodevelopmental disorder and immunodeficiency. *LymphoSign Journal*. https://doi.org/10.14785/lymphosign-2023-0008

Serra, I., Koning, M., Van Der Spek, P. J., Dalm, V. A. S. H., & Badura, A. (2025). Analysis of genetic overlap between inborn errors of immunity and neurodevelopmental disorders. https://doi.org/10.1101/2025.03.01.25323148

Van Den Noortgate, M., Morrens, M., Foiselle, M., & De Picker, L. (2025). Immune dysregulation in psychiatric disorders with and without exposure to childhood maltreatment: A transdiagnostic stratified meta-analysis.. *Brain, behavior, and immunity*. https://doi.org/10.1016/j.bbi.2025.03.002

Xiao, N., Huang, X., Chen, L., Zang, W., Guan, M., Li, T., Tuzankina, I., Chereshnev, V., & Liu, G. (2025). Neurological Complications in Inborn Errors of Immunity: A Scoping Review of Clinical Spectrum, Pathophysiological Mechanisms, and Therapeutic Strategies. *Clinical Reviews in Allergy & Immunology, 68*. https://doi.org/10.1007/s12016-025-09078-7

Xiu, Z., Sun, L., Cao, H., Qu, H.-Q., Glessner, J., Ding, Z., Zheng, G., Wang, N., Xia, Q., Li, J., Hakonarson, H., Liu, W., & Li, J. (2024). Shared molecular mechanisms and transdiagnostic potential of neurodevelopmental disorders and immune disorders.. *Brain, behavior, and immunity*. https://doi.org/10.1016/j.bbi.2024.04.026

Yiu, E., Dissanayake, D., Cunningham, J., Branson, H., Scott, O., & Yeh, E. (2026). Inborn errors of immunity in children with neuroinflammation.. *Developmental medicine and child neurology*. https://doi.org/10.1111/dmcn.70365