With respect to Paternal biological contributions to Neurodevelopmental and Psychiatric Disorders, what is the current research on Paternal Immune Activation and Paternal Germline Mutations?

Paternal Immune Activation and **Germline Mutations** in Neurodevelopmental Disorders

Research on paternal biological contributions to neurodevelopmental and psychiatric disorders spans two distinct facets: paternal immune activation and paternal germline mutations. The evidence base for paternal immune activation is notably thinner than for maternal immune activation, with most studies finding null or weak paternal effects. Paternal germline mutations, particularly those associated with advanced paternal age, represent a more established contributor to offspring neurodevelopmental risk.

Paternal Immune Activation

The dominant research focus has been on **maternal immune activation** (MIA), with paternal immune activation receiving comparatively little direct investigation (Kwon et al., 2022; Han et al., 2021). A large Swedish cohort study of over 4.2 million offspring specifically tested whether parental primary immunodeficiencies (PIDs) — as a natural experiment for immune dysregulation — were associated with psychiatric outcomes in offspring. Maternal PIDs significantly increased offspring risk of any psychiatric disorder (IRR 1.17) and suicidal behavior (IRR 1.20), but **paternal PIDs showed no significant association** with either outcome (IRR 1.03 and 1.10, respectively) (Isung et al., 2023). This asymmetry supports the MIA hypothesis as a primarily maternal mechanism and suggests paternal immune dysregulation does not confer comparable in-utero neurodevelopmental risk (Isung et al., 2023).

Comparison	Maternal PID	Paternal PID
Any psychiatric disorder (IRR)	1.17 (1.10–1.25)	1.03 (0.94–1.14)
Suicidal behavior (IRR)	1.20 (1.06–1.36)	1.10 (0.91–1.34)
Combined PID + autoimmune risk	1.24 (1.11–1.38)	Not significant

FIGURE 1 Maternal vs. paternal immunodeficiency associations with offspring psychiatric outcomes from a Swedish cohort of 4.2 million offspring

A separate study comparing maternal and paternal polygenic scores for ADHD, autism, and schizophrenia found associations were **largely consistent between parents** for pregnancy-related measures, suggesting that some previously attributed maternal causal effects may reflect shared genetic confounding from either parent (Havdahl et al., 2022). This finding implies paternal genetic liability can confound associations previously thought to be exclusively maternal, though it does not address paternal immune activation per se.

Paternal Germline Mutations

Advanced paternal age (APA) is the most studied source of paternal germline mutations linked to neurodevelopmental disorders. Aging-related **free radical damage** causes accumulation of DNA-level changes and epigenetic modifications in the male reproductive system and spermatozoa, ultimately increasing offspring NDD risk (Yan et al., 2024). Epidemiological data link older paternal age to increased risk for autism spectrum disorder and schizophrenia (Hall et al., 2023).

Key mechanisms identified in the literature include:

- **De novo germline mutations** accumulate with paternal age and are selectively enriched for NDD-related genes (Yan et al., 2024).
- **Epigenetic modifications** in sperm, including altered DNA methylation, may transmit disease-relevant regulatory changes (Yan et al., 2024).
- Current studies are largely restricted to **univariate approaches**, and multi-mechanism synergistic effects remain underexplored (Yan et al., 2024).

Parent-of-origin effects add further complexity. For 15q11-q13 duplications, **paternally inherited copies** are associated with normal or milder phenotypes (mild learning difficulties, dyslexia), while maternally inherited duplications consistently produce more severe neurodevelopmental anomalies including intellectual impairment, epilepsy, and psychiatric disorders (Parijs et al., 2023). This imprinting-based asymmetry demonstrates that the same paternal germline structural variant can have markedly different consequences depending on parent of origin.

Studies of parental trait transmission also reveal paternal-specific patterns. In families with multiple autistic children (multiplex), **fathers show elevated autistic traits** compared to parents of non-autistic children, while simplex fathers do not differ from controls (Mullin et al., 2026). Parental traits jointly account for approximately 7.9% of autism recurrence liability in multiplex families (Mullin et al., 2026), and the correlation structure between autistic and neuropsychiatric traits differs between simplex and multiplex parents, suggesting distinct inheritance patterns (Mullin et al., 2026).

Research Gaps and Limitations

The evidence base reveals a striking imbalance: the vast majority of immune activation research focuses on maternal mechanisms, with paternal immune activation largely untested as an independent exposure (Isung et al., 2023). Paternal germline mutation research is dominated by APA-associated de novo mutations, while other sources of paternal germline variation — environmental toxicant exposure, infection-induced sperm DNA damage, or non-age-related epigenetic shifts — receive limited attention (Yan et al., 2024). The field would benefit from studies that directly measure paternal inflammatory biomarkers and sperm quality in relation to offspring neurodevelopmental outcomes, rather than relying on maternal-focused designs with paternal data as negative controls.

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