Advanced paternal age, paternal immune activation and Neurodevelopmental and Psychiatric Disorders?

Advanced paternal age, paternal immune activation, and brain disorders: what the studies show

Research links **advanced paternal age (APA)** and **parental immune activation** to higher risk of neurodevelopmental and psychiatric disorders in offspring, but via partly different, interacting mechanisms.

Effects of advanced paternal age

- Large population cohorts show older fathers have higher-risk children for **autism, ADHD, schizophrenia, bipolar disorder, depression, substance use, intellectual disability, and suicide attempts**, often with dose–response increases above ~45 years (D'Onofrio et al., 2014; De Kluiver et al., 2016; Wang et al., 2022; Yatsenko & Turek, 2018; Kaltsas et al., 2023).
- A Taiwanese cohort of 7.3 million births found older paternal age (>25, especially higher brackets) was linearly associated with schizophrenia, autism, bipolar disorder, ADHD, anxiety, OCD, intellectual disability, substance use, and suicide (Wang et al., 2022).
- Within-family (sibling) designs confirm the association and suggest a **causal component**, not just social confounding (D'Onofrio et al., 2014; Wang et al., 2022).

Main proposed mechanisms

Mechanism	Key points	Citations
De novo mutations	dnSNVs increase with paternal age but explain only a **small part** of risk for ASD, intellectual disability, epilepsy-NDD, SCZ; ASD/SCZ epidemiology suggests other factors too (Taylor et al., 2017; Gratten et al., 2016).	(Taylor et al., 2017; Gratten et al., 2016)
Epigenetic changes	Aging sperm shows **clustered DNA methylation abnormalities**, transmitted to blastocysts and enriched in genes for autism, schizophrenia, bipolar disorder (Weber-Stadlbauer et al., 2016).	(Weber-Stadlbauer et al., 2016)
RNA / microRNA changes	APA mice show autism-like behavior, with altered miR-132/miR-134; humans with APA show differential DNA methylation and brain structural changes (Krug et al., 2020).	(Krug et al., 2020)
Selection / liability	Models indicate shared familial psychiatric liability and selection into late fatherhood can explain much APA–risk association (Janecka et al., 2017; De Kluiver et al., 2016; Gratten et al., 2016; Wang et al., 2022).	(Janecka et al., 2017; De Kluiver et al., 2016; Gratten et al., 2016; Wang et al., 2022)

FIGURE 1 Mechanisms proposed to link paternal age and offspring brain disorders.

Paternal immune activation and immune-mediated pathways

- Most empirical work is on **maternal immune activation (MIA)**: prenatal inflammation (infection, obesity, autoimmune disease, stress) increases risk of ASD, ADHD, Tourette and other NDDs; animal models show lasting microglial and synaptic abnormalities and behavioral changes (Han et al., 2021; Gumusoglu & Stevens, 2019; Boulanger-Bertolus et al., 2018; Bergdolt & Dunaevsky, 2019; Mueller et al., 2020).
- A mouse MIA study showed **transgenerational, paternally mediated** transmission of social deficits, altered fear, despair-like behavior, and brain transcriptional changes up to the F3 generation, without further immune challenge (Vervoort et al., 2021).
- A recent hypothesis paper argues that **paternal immune activation (PIA)** is plausibly as important as MIA for schizophrenia risk, likely via **epigenetic changes in sperm** rather than direct cytokine exposure, but emphasizes that **empirical human PIA data are currently lacking** (Debnath & Berk, 2023).

Interaction: advanced paternal age, epigenetics, and immune/neuroinflammatory changes

- APA sperm and embryos from older fathers show altered methylomes at neurodevelopmental genes, supporting **non-genetic paternal transmission of vulnerability** (Weber-Stadlbauer et al., 2016).
- In an APA mouse model, offspring display autism-like behaviors, cognitive deficits, and heightened **neuroinflammation mediated by microglial overactivation**; this is linked to aberrant m6A RNA methylation (Nr4a2, Ythdc1) in sperm and offspring hippocampus, and can be partly reversed by targeting Ythdc1 (Mao et al., 2024).
- Reviews propose **multifactorial models** where male aging, de novo mutations, epigenetic drift, psychosocial factors, and broader environment (including parental immune status) act together to shape risk (Janecka et al., 2017; Gumusoglu & Stevens, 2019; Vervoort et al., 2021; Yan et al., 2024).

Conclusion

Advanced paternal age is consistently associated with higher risk of a broad spectrum of neurodevelopmental and psychiatric disorders, with contributions from de novo mutations but substantial roles for **epigenetic and familial liability**. Immune-mediated mechanisms, well established for maternal immune activation and experimentally for transgenerational, paternally transmitted effects, likely intersect with APA-related epigenetic changes and neuroinflammation. For **paternal immune activation specifically**, current support is largely theoretical or from animal work; robust human data remain a key research gap.

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