Does Mitochondrial DNA copy number increase as mitochondria become progressively dysregulated in Neurodevelopmental and Psychiatric Disorders?

Yes, **mtDNA copy number increases** as a compensatory response to mitochondrial dysregulation, though directionality varies by disorder, tissue, and stage.

Does mitochondrial DNA copy number increase as mitochondria become progressively dysregulated in neurodevelopmental and psychiatric disorders? N = 6

Yes 83% · Possibly 17% · Mixed 0% · No 0%

FIGURE 1 Research consensus on mtDNA copy number increase in neuropsychiatric disorders

A substantial body of evidence indicates that elevated mtDNA copy number (mtDNA-CN) reflects a **compensatory biogenesis response** to oxidative stress and defective mitochondria across multiple neurodevelopmental and psychiatric conditions (Al-Kafaji et al., 2023; Li et al., 2018; Bam et al., 2021). The pattern is not universal, however: peripheral blood often shows decreased or unchanged mtDNA-CN even when brain tissue shows increases, and some disorders exhibit the opposite direction (Das et al., 2022; Li et al., 2018).

Evidence for Compensatory mtDNA-CN Elevation

Evidence Strength	Claim
Strong	Elevated mtDNA-CN is a **compensatory response** to oxidative stress and energy deficit, observed across ASD, ADHD, MDD, and BD (Al-Kafaji et al., 2023; Meloni et al., 2024; Bam et al., 2021).
Moderate	Postmortem brain tissue from schizophrenia and bipolar patients shows **increased mtDNA-CN** in the dorsolateral prefrontal cortex, while peripheral blood shows decreased levels (Das et al., 2022).
Moderate	Meta-analysis confirms elevated mtDNA-CN in ASD and ADHD in **non-blood tissues** but not consistently in peripheral blood (Al-Kafaji et al., 2023).
Moderate	Mood-state-dependent changes show **decreased mtDNA-CN** in manic and depressive bipolar patients, and BD type I patients have lower copy numbers than controls (Li et al., 2018; Chung et al., 2020).

FIGURE 2 Evidence strength for mtDNA-CN elevation claims across neuropsychiatric disorders

Compensatory Mechanism in Neurodevelopmental Disorders

The core mechanism proposed across studies is that oxidative stress damages mtDNA, impairing electron transport chain function and creating an energy deficit. Cells respond by upregulating mtDNA replication to increase mitochondrial copy number, attempting to compensate for defective mitochondria (Al-Kafaji et al., 2023; Li et al., 2018). In autism, frontal cortex tissue shows increased copy numbers of mitochondrial genes ND1, ND4, and CytB alongside significantly reduced activities of ETC complexes I, V, and pyruvate dehydrogenase, directly linking the copy-number increase to measurable bioenergetic impairment (Gu et al., 2013).

This compensation hypothesis is further supported by the finding that mtDNA-CN correlates positively with mtDNA deletions in ASD, indicating that higher copy number tracks with greater mitochondrial damage (Bam et al., 2021). ADHD patients similarly show **1.3-fold higher mtDNA-CN** than controls, consistent with a reactive biogenesis response (Citrigno et al., 2025).

Tissue- and Disorder-Specific Discrepancies

The relationship between mtDNA-CN and dysregulation is **not uniformly positive**. Key sources of variability include tissue type, mood state, medication exposure, and disorder subtype.

- **Brain vs. blood discordance**: Schizophrenia and bipolar disorder show increased mtDNA-CN in DLPFC brain tissue but decreased mtDNA-CN in peripheral blood, likely reflecting the brain's higher bioenergetic demand (Das et al., 2022).
- **Bipolar mood-state effects**: Manic and depressive bipolar patients show significantly decreased peripheral mtDNA-CN, while euthymic patients do not differ from controls, and copy number correlates negatively with number of relapses (Li et al., 2018).
- **BD subtype divergence**: BD type I patients have lower mtDNA-CN than controls, while BD type II patients have higher mtDNA-CN, suggesting distinct mitochondrial pathophysiologies (Chung et al., 2020).
- **Medication confounding**: Antipsychotic users with schizophrenia have significantly higher mtDNA-CN than non-users, and lithium treatment in BD is associated with lower mtDNA-CN compared to other mood stabilizers (Bulduk et al., 2024; Meloni et al., 2024).

Genetic Causality and Shared Architecture

Mendelian randomization studies provide mixed evidence on causal directionality. Higher genetically determined mtDNA-CN is associated with **reduced ASD risk** (OR ≈ 0.73–0.80), suggesting that greater mitochondrial copy number may be protective rather than merely a marker of dysfunction (Qiu et al., 2025; Lu et al., 2024; Niu et al., 2024). A separate MR analysis found negative causal effects of mtDNA-CN on bipolar disorder, Alzheimer's, dementia, depressive symptoms, and ASD, while anxiety disorders showed a reverse causal effect increasing mtDNA-CN (Fu et al., 2025; Niu et al., 2024).

Genetic overlap analyses reveal significant global-level shared architecture between mtDNA-CN and all five major psychiatric disorders (ADHD, ASD, BD, MDD, SCZ), with 87 shared genes exhibiting downregulation in key brain regions and enrichment in neurodevelopmental pathways (Xue et al., 2026). This shared genetic architecture reinforces that mitochondrial function and psychiatric risk are mechanistically linked, though the direction of mtDNA-CN change depends on context rather than following a single progressive trajectory.

In summary, mtDNA-CN frequently increases as a compensatory response to mitochondrial dysregulation in neurodevelopmental and psychiatric disorders, particularly in brain tissue and in ASD and ADHD. However, the relationship is bidirectional and context-dependent: peripheral blood, manic bipolar states, BD type I, and medication effects can produce decreased or unchanged copy numbers despite underlying mitochondrial dysfunction.

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