Mitochondrial Dysfunction in Psychiatric and Neurodevelopmental Disorders: A Comprehensive Review

1. Introduction

Mitochondrial dysfunction has emerged as a significant factor implicated in a wide range of psychiatric and neurodevelopmental disorders, including autism spectrum disorder (ASD), schizophrenia, depression, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), and intellectual disability (Payares et al., 2024; Frye et al., 2024; Ni et al., 2022; Yang et al., 2025; Ortiz-González, 2021; Tanaka et al., 2022; Rezin et al., 2009; Marazziti et al., 2012; Jiang et al., 2024; Rossignol & Frye, 2011; Rajasekaran et al., 2015). Evidence from systematic reviews, genetic studies, biomarker analyses, and animal models consistently demonstrates that abnormalities in mitochondrial function—such as impaired oxidative phosphorylation, altered mitochondrial DNA (mtDNA), disrupted dynamics (fusion/fission), and increased oxidative stress—are associated with both the onset and progression of these disorders (Payares et al., 2024; Frye et al., 2024; Ni et al., 2022; Yang et al., 2025; Ortiz-González, 2021). While ASD has received the most research attention, mitochondrial dysfunction is also observed in other neurodevelopmental and psychiatric conditions, often correlating with symptom severity and comorbidities (Payares et al., 2024; Frye et al., 2024; Yang et al., 2025). However, questions remain regarding causality versus association, specificity to particular disorders, and the potential for targeted therapeutic interventions (Anitha et al., 2023; Ortiz-González, 2021; Papageorgiou & Filiou, 2024). The following review synthesizes current findings on the role of mitochondrial dysfunction across these conditions.

Is mitochondrial dysfunction associated with psychiatric and neurodevelopmental disorders? N = 48

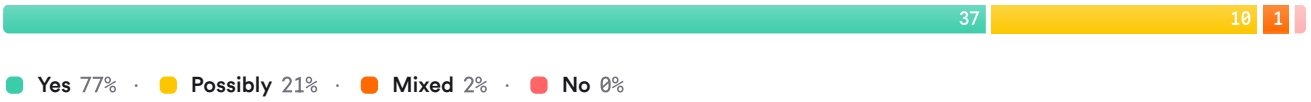

FIGURE 1 Consensus meter visualizing agreement on the association between mitochondrial dysfunction and psychiatric/neurodevelopmental disorders.

2. Methods

A comprehensive literature search was conducted across over 170 million research papers in Consensus, encompassing databases such as Semantic Scholar and PubMed. The search strategy included foundational theories, disorder-specific focus (e.g., ASD, schizophrenia, ADHD), alternate terminology (e.g., oxidative stress), contrasting perspectives on causality/significance, interdisciplinary expansion (e.g., genetics, metabolism), and therapeutic approaches. In total, 3,691,642 papers were identified; after relevance filtering and deduplication, 143 papers were screened for eligibility. Of these, 50 were included in this review.

Search Strategy

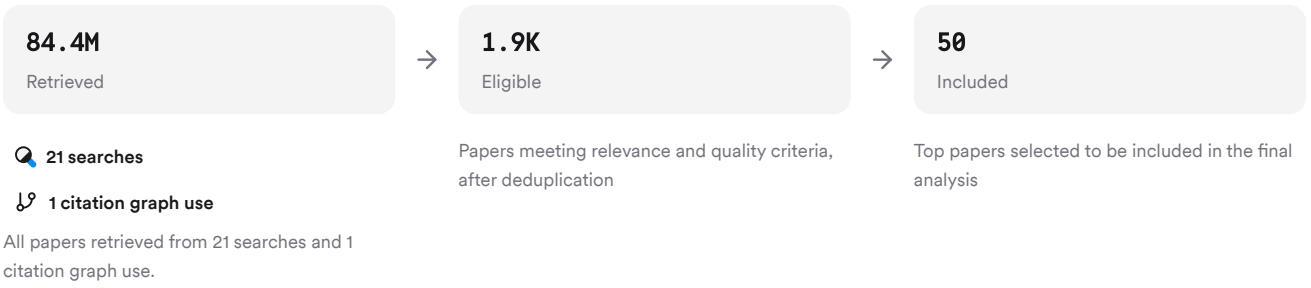

FIGURE 2 Flow diagram of paper identification to inclusion for this review.

Six unique search strategies were used to ensure broad coverage of foundational theories, specific disorders, mechanisms/biomarkers, critiques/debates on causality, interdisciplinary links, and therapeutic interventions.

3. Results

3.1 Overview of Mitochondrial Dysfunction Across Disorders

Multiple studies confirm that mitochondrial dysfunction is prevalent in ASD (Payares et al., 2024; Frye et al., 2024; Hollis et al., 2017; Rossignol & Frye, 2011; Rose et al., 2018), schizophrenia (Ni et al., 2022; Morén et al., 2025; Ni & Chung, 2020; Rajasekaran et al., 2015), depression (Rezin et al., 2009; Jiang et al., 2024), bipolar disorder (Rezin et al., 2009), ADHD (Payares et al., 2024; Giannoulis et al., 2022; Almutairi et al., 2024; Öğütlü et al., 2022), Rett syndrome (Yang et al., 2025), Fragile X syndrome (Upaganlawar et al., 2022), Down syndrome (Valenti & Vacca, 2023), intellectual disability (Ortiz-González, 2021), and other neurodevelopmental conditions. Common features include impaired energy metabolism (ATP production), increased oxidative stress markers (lactate/pyruvate), mtDNA mutations or copy number changes, abnormal mitochondrial morphology/dynamics (fusion/fission defects), and altered neurotransmitter metabolism (Payares et al., 2024; Frye et al., 2024; Ni et al., 2022; Yang et al., 2025).

3.2 Disorder-Specific Findings

- **Autism Spectrum Disorder (ASD):** Elevated prevalence of mitochondrial disease (~5% vs. ~0.01% general population) and widespread biomarker abnormalities are reported in ASD populations (Frye et al., 2024; Rossignol & Frye, 2011). Mitochondrial dysfunction correlates with clinical features such as developmental regression, seizures, gastrointestinal symptoms, motor delays, fatigue/lethargy, and ASD severity (Frye et al., 2024; Rossignol & Frye, 2011). Both primary genetic defects and secondary/environmentally induced dysfunctions are implicated (Rose et al., 2018).
- **Schizophrenia:** Multiple lines of evidence—including postmortem brain studies—show reduced activity of electron transport chain complexes (notably complex I), decreased mtDNA content/expression in affected brain regions/cell types (pyramidal neurons/oligodendrocytes), increased oxidative stress/inflammation markers, and altered bioenergetics during development (Ni et al., 2022; Morén et al., 2025; Ni & Chung, 2020; Rajasekaran et al., 2015).
- **Depression & Bipolar Disorder:** Impaired brain energy metabolism/mitochondrial quality control systems are observed in both clinical samples and animal models; antidepressants may exert effects by improving mitochondrial function (Rezin et al., 2009; Jiang et al., 2024). Mitochondrial dysfunction is linked to synaptic impairment/neuroinflammation in depression (Song et al., 2023).
- **ADHD:** Genetic variation in mtDNA/nuclear-encoded genes is associated with ADHD pathophysiology; increased mtDNA copy number may compensate for hereditary/environmental insults; severity reduction correlates with improved mitochondrial function post-treatment (Giannoulis et al., 2022; Almutairi et al., 2024).
- **Other Neurodevelopmental Disorders:** Rett syndrome/Fragile X/Down syndrome all show evidence of bioenergetic deficits contributing to cognitive impairment/intellectual disability via disrupted neurogenesis/neuroplasticity pathways (Yang et al., 2025; Valenti & Vacca, 2023).

3.3 Mechanisms & Pathways

Key mechanisms include:

- Impaired oxidative phosphorylation/ATP production
- Increased reactive oxygen species (ROS) leading to oxidative damage
- Disrupted calcium homeostasis/apoptosis regulation
- Abnormal mitophagy/autophagic clearance
- Genetic mutations/deletions affecting mtDNA or nuclear genes encoding mitochondrial proteins
- Environmental factors/toxicants modulating mitochondrial function These mechanisms converge on neuronal dysfunction affecting cognition/emotion/behavior across disorders (Payares et al., 2024; Ni et al., 2022; Yang et al., 2025).

3.4 Therapeutic Approaches & Biomarkers

Emerging therapies target mitochondria directly: antioxidants/cofactors (L-carnitine/coenzyme Q10/ubiquinol), ketogenic diet/interventions enhancing mitophagy or biogenesis show promise especially in ASD but require further validation across disorders (Frye, 2020). Biomarkers such as lactate/pyruvate ratios or mtDNA copy number may aid diagnosis/prognosis but lack specificity/sensitivity for routine clinical use at present (Frye et al., 2024).

Results Timeline

Results Timeline

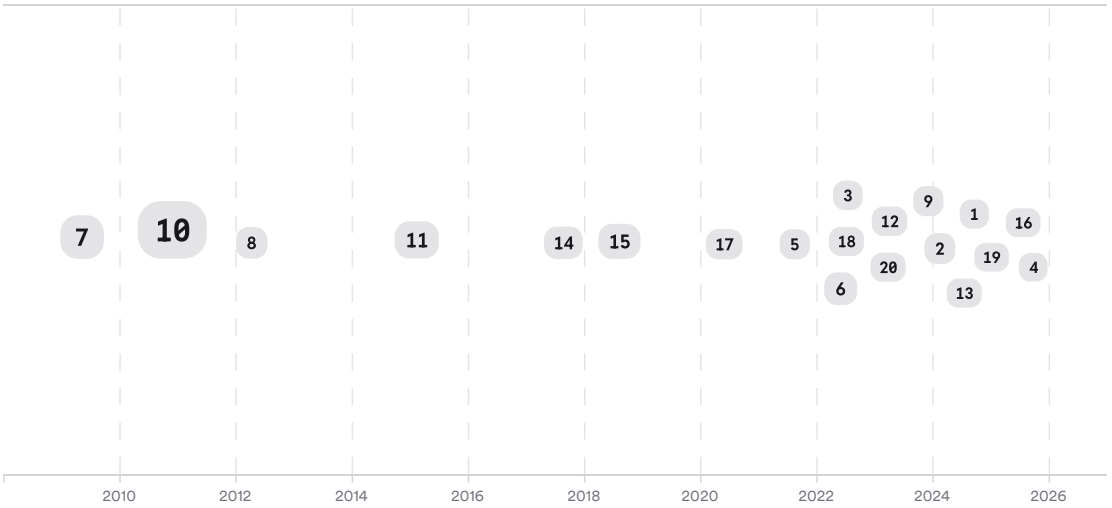

FIGURE 3 Timeline showing publication trends on mitochondrial dysfunction across psychiatric/neurodevelopmental disorders. Larger markers indicate more citations.

Top Contributors

Type	Name	Papers
Author	R. Frye	(Ni et al., 2022; Morén et al., 2025; Kim et al., 2019; Roberts, 2020; Frye et al., 2024)
Author	D. Rossignol	(Morén et al., 2025; Kim et al., 2019)
Author	Peiyan Ni	(Yang et al., 2025; Anitha et al., 2023)
Journal	*Molecular Psychiatry*	(Morén et al., 2025; Cuénod et al., 2021)
Journal	*Frontiers in Psychiatry*	(Payares et al., 2024; Almutairi et al., 2024)
Journal	*Neuroscience & Biobehavioral Reviews*	(Ni & Chung, 2020; Giannoulis et al., 2022)

FIGURE 4 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The literature robustly supports an association between mitochondrial dysfunction and a spectrum of psychiatric/neurodevelopmental disorders—most notably ASD and schizophrenia—though causality remains debated for many conditions (Payares et al., 2024; Anitha et al., 2023; Ortiz-González, 2021). The strongest evidence comes from biomarker studies/meta-analyses showing higher rates of biochemical abnormalities among affected individuals compared to controls; genetic studies further implicate both inherited/acquired mtDNA mutations as risk factors for disease development/severity (Frye et al., 2024; Ortiz-González, 2021). However:

- Many findings are correlative rather than causal; it remains unclear whether mitochondrial dysfunction is a primary driver or a downstream effect of disease processes or environmental/lifestyle factors such as chronic stress or medication use (Anitha et al., 2023; Morella et al., 2022).
- There is considerable heterogeneity within/between disorders regarding which aspects of mitochondrial biology are affected —suggesting circuit-, cell-, or stage-specific vulnerabilities rather than a universal mechanism for all psychiatric illness (Kim et al., 2019).
- Most research focuses on ASD; other conditions like ADHD or mood disorders are less well-studied but show emerging evidence for similar mechanisms. Therapeutically targeting mitochondria holds promise but requires more rigorous clinical trials to establish efficacy/safety beyond preliminary findings from small-scale studies or animal models.

Claims & Evidence Table

Claim	Evidence Strength	Reasoning	Papers
Mitochondrial dysfunction is associated with ASD	Strong	Supported by multiple meta-analyses/reviews showing high prevalence of biomarkers/genetic variants among ASD patients	(Payares et al., 2024), (Frye et al., 2024), (Rossignol & Frye, 2011), (Rose et al., 2018), (Frye, 2020)
Schizophrenia involves impaired mitochondrial function	Strong	Postmortem/genetic/imaging studies consistently show ETC deficits/oxidative stress/inflammation	(Ni et al., 2022), (Morén et al., 2025), (Ni & Chung, 2020), (Rajasekaran et al., 2015), (Ben-Shachar, 2017), (Roberts, 2020)
Depression/bipolar disorder linked to energy metabolism deficits	Strong	Clinical/animal model data support impaired ATP production/mitochondrial quality control involvement	(Rezin et al., 2009), (Jiang et al., 2024), (Khan et al., 2023), (Song et al., 2023)
ADHD shows genetic variation affecting mitochondria	Moderate	Systematic reviews/meta-analysis report associations between mtDNA/nuclear gene variants & ADHD risk/severity	(Giannoulis et al., 2022), (Almutairi et al., 2024), (Öğütlü et al., 2022)
Causality between mitochondrial dysfunction & psychiatric symptoms remains unclear	Moderate	Many studies are correlative; reverse causation/lifestyle confounders possible; more longitudinal/interventional data needed	(Anitha et al., 2023), (Ortiz-González, 2021), (Morella et al., 2022)
Targeted therapies improve some symptoms but lack robust clinical validation	Moderate	Preliminary trials suggest benefit from antioxidants/cofactors/dietary interventions but large RCTs lacking	(Frye, 2020)

FIGURE Key claims and support evidence identified in these papers.

5. Conclusion

Current evidence strongly supports an association between **mitochondrial dysfunction** and a range of **psychiatric** and **neurodevelopmental disorders**, particularly ASD and schizophrenia. While mechanistic links are increasingly understood—including impaired energy metabolism/oxidative stress/genetic mutations—the directionality/specificity of these relationships remains under investigation. Targeted therapies hold promise but require further validation.

Research Gaps

Despite substantial progress:

- Most research focuses on ASD; other neurodevelopmental/psychiatric conditions remain understudied.
- Causality versus correlation is unresolved.
- Biomarkers lack specificity/sensitivity for routine clinical use.
- Large-scale interventional trials targeting mitochondria are rare.

Research Gaps Matrix

Topic/Outcome	ASD	Schizophrenia	Depression/Bipolar	ADHD
Biomarker studies	7	5	2	2
Genetic associations	6	4	2	2
Therapeutic trials	4	2	1	GAP
Mechanistic models	8	7	4	2

FIGURE Matrix highlighting gaps by topic/outcome versus disorder type.

Open Research Questions

Future research should clarify causality/mechanisms underlying these associations through longitudinal/interventional designs; expand biomarker discovery; validate targeted therapies; explore underrepresented conditions/populations.

Question	Why
Does correcting mitochondrial dysfunction improve core symptoms across different psychiatric/neurodevelopmental disorders?	Direct interventional trials will clarify if targeting mitochondria yields meaningful clinical benefits beyond correlation alone.
What are the circuit-, cell-, or developmental stage-specific vulnerabilities to mitochondrial impairment?	Understanding specificity will enable precision medicine approaches tailored to individual risk profiles/disorders.
Can reliable biomarkers be developed for early detection or prognosis based on mitochondrial function?	Early identification could enable preventive interventions before irreversible damage occurs in at-risk populations.

FIGURE Open questions guiding future research directions.

In summary: Mitochondrial dysfunction is a common thread linking diverse psychiatric/neurodevelopmental syndromes—but much work remains to translate this knowledge into precise diagnostics or effective treatments across the full spectrum of mental health conditions.

References

Almutairi, M., Althekair, A., Almutairi, F., Alatabani, M., & Alsaikhan, A. (2024). Mitochondrial dysfunction and mitophagy in ADHD: Cellular and molecular mechanisms. *Saudi Pharmaceutical Journal : SPJ, 32*. https://doi.org/10.1016/j.jsps.2024.102212

Anitha, A., Thanseem, I., Iype, M., & Thomas, S. (2023). Mitochondrial dysfunction in cognitive neurodevelopmental disorders: Cause or effect?. *Mitochondrion*. https://doi.org/10.1016/j.mito.2023.01.002

Ben-Shachar, D. (2017). Mitochondrial multifaceted dysfunction in schizophrenia; complex I as a possible pathological target. *Schizophrenia Research, 187*, 3-10. https://doi.org/10.1016/j.schres.2016.10.022

Cuénod, M., Steullet, P., Cabungcal, J., Dwir, D., Khadimallah, I., Klauser, P., Conus, P., & , K. (2021). Caught in vicious circles: a perspective on dynamic feed-forward loops driving oxidative stress in schizophrenia. *Molecular Psychiatry, 27*, 1886 - 1897. https://doi.org/10.1038/s41380-021-01374-w

Frye, R., Rincon, N., McCarty, P., Brister, D., Scheck, A., & Rossignol, D. (2024). Biomarkers of mitochondrial dysfunction in autism spectrum disorder: A systematic review and meta-analysis.. *Neurobiology of disease*, 106520. https://doi.org/10.1016/j.nbd.2024.106520

Frye, R. (2020). Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and Targeted Treatments.. *Seminars in pediatric neurology, 35*, 100829. https://doi.org/10.1016/j.spen.2020.100829

Frye, R., McCarty, P., Werner, B., Rose, S., & Scheck, A. (2024). Bioenergetic signatures of neurodevelopmental regression. *Frontiers in Physiology, 15*. https://doi.org/10.3389/fphys.2024.1306038

Giannoulis, S., Müller, D., Kennedy, J., & Gonçalves, V. (2022). Systematic review of mitochondrial genetic variation in attention-deficit/hyperactivity disorder. *European Child & Adolescent Psychiatry, 33*, 1675 - 1685. https://doi.org/10.1007/s00787-022-02030-6

Hollis, F., Kanellopoulos, A., & Bagni, C. (2017). Mitochondrial dysfunction in Autism Spectrum Disorder: clinical features and perspectives. *Current Opinion in Neurobiology, 45*, 178-187. https://doi.org/10.1016/j.conb.2017.05.018

Jiang, M., Wang, L., & Sheng, H. (2024). Mitochondria in depression: The dysfunction of mitochondrial energy metabolism and quality control systems. *CNS Neuroscience & Therapeutics, 30*. https://doi.org/10.1111/cns.14576

Khan, M., Baussan, Y., & Hebert-Chatelain, E. (2023). Connecting Dots between Mitochondrial Dysfunction and Depression. *Biomolecules, 13*. https://doi.org/10.3390/biom13040695

Kim, Y., Vadodaria, K., Lenkei, Z., Kato, T., Gage, F., Marchetto, M., & Santos, R. (2019). Mitochondria, Metabolism, and Redox Mechanisms in Psychiatric Disorders. *Antioxidants & Redox Signaling, 31*, 275 - 317. https://doi.org/10.1089/ars.2018.7606

Marazziti, D., Baroni, S., Picchetti, M., Landi, P., Silvestri, S., Vatteroni, E., & CatenaDell'Osso, M. (2012). Psychiatric disorders and mitochondrial dysfunctions.. *European review for medical and pharmacological sciences, 16 2*, 270-5.

Morella, I., Brambilla, R., & Morè, L. (2022). Emerging roles of brain metabolism in cognitive impairment and neuropsychiatric disorders.. *Neuroscience and biobehavioral reviews*, 104892. https://doi.org/10.1016/j.neubiorev.2022.104892

Morén, C., Olivares-Berjaga, D., Martínez-Pinteño, A., Bioque, M., Rodríguez, N., Gassó, P., Martorell, L., & Parellada, E. (2025). Mitochondrial Oxidative Phosphorylation System Dysfunction in Schizophrenia. *International Journal of Molecular Sciences, 26*. https://doi.org/10.3390/ijms26094415

Ni, P., , Y., & Chung, S. (2022). Mitochondrial dysfunction in psychiatric disorders.. *Schizophrenia research*. https://doi.org/10.1016/j.schres.2022.08.027

Ni, P., & Chung, S. (2020). Mitochondrial Dysfunction in Schizophrenia. *BioEssays, 42*. https://doi.org/10.1002/bies.201900202

Öğütlü, H., Kaşak, M., & Tabur, S. (2022). Mitochondrial Dysfunction in Attention Deficit Hyperactivity Disorder. *The Eurasian Journal of Medicine, 54*, S187 - S195. https://doi.org/10.5152/eurasianjmed.2022.22187

Ortiz-González, X. (2021). Mitochondrial Dysfunction: A Common Denominator in Neurodevelopmental Disorders?. *Developmental Neuroscience, 43*, 222 - 229. https://doi.org/10.1159/000517870

Papageorgiou, M., & Filiou, M. (2024). Mitochondrial dynamics and psychiatric disorders: The missing link.. *Neuroscience and biobehavioral reviews*, 105837. https://doi.org/10.1016/j.neubiorev.2024.105837

Payares, D., Spooner, L., Vosters, J., Dominguez, S., Patrick, L., Harris, A., & Kanungo, S. (2024). A systematic review on the role of mitochondrial dysfunction/disorders in neurodevelopmental disorders and psychiatric/behavioral disorders. *Frontiers in Psychiatry, 15*. https://doi.org/10.3389/fpsyt.2024.1389093

Rajasekaran, A., Venkatasubramanian, G., Berk, M., & Debnath, M. (2015). Mitochondrial dysfunction in schizophrenia: Pathways, mechanisms and implications. *Neuroscience & Biobehavioral Reviews, 48*, 10-21. https://doi.org/10.1016/j.neubiorev.2014.11.005

Rezin, G., Amboni, G., Zugno, A., Quevedo, J., & Streck, E. (2009). Mitochondrial Dysfunction and Psychiatric Disorders. *Neurochemical Research, 34*, 1021-1029. https://doi.org/10.1007/s11064-008-9865-8

Roberts, R. (2020). Mitochondrial dysfunction in schizophrenia: with a focus on postmortem studies.. *Mitochondrion*. https://doi.org/10.1016/j.mito.2020.11.009

Rose, S., Niyazov, D., Rossignol, D., Goldenthal, M., Kahler, S., & Frye, R. (2018). Clinical and Molecular Characteristics of Mitochondrial Dysfunction in Autism Spectrum Disorder. *Molecular Diagnosis & Therapy, 22*, 571 - 593. https://doi.org/10.1007/s40291-018-0352-x

Rossignol, D., & Frye, R. (2011). Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. *Molecular Psychiatry, 17*, 290 - 314. https://doi.org/10.1038/mp.2010.136

Song, Y., Cao, H., Zuo, C., Gu, Z., Huang, Y., Miao, J., Fu, Y., Guo, Y., Jiang, Y., & Wang, F. (2023). Mitochondrial dysfunction: A fatal blow in depression.. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 167*, 115652. https://doi.org/10.1016/j.biopha.2023.115652

Tanaka, M., Szabó, Á., Spekker, E., Polyák, H., Tóth, F., & Vécsei, L. (2022). Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan–Kynurenine Metabolic System. *Cells, 11*. https://doi.org/10.3390/cells11162607

Upaganlawar, A., Gawali, S., Marde, V., Kale, N., Dhokne, M., Kale, M., Wankhede, N., Taksande, B., & Umekar, M. (2022). Mitochondrial Dysfunction in Neurodevelopmental Disorders: A Systematic Review on Pathways and Mechanisms. *Current Indian Science*. https://doi.org/10.2174/2210299x02666221107151717

Valenti, D., & Vacca, R. (2023). Brain Mitochondrial Bioenergetics in Genetic Neurodevelopmental Disorders: Focus on Down, Rett and Fragile X Syndromes. *International Journal of Molecular Sciences, 24*. https://doi.org/10.3390/ijms241512488

Yang, Z., Luo, Y., Yang, Z., Liu, Z., Li, M., Wu, X., Chen, L., & Xin, W. (2025). Mitochondrial dynamics dysfunction and neurodevelopmental disorders: From pathological mechanisms to clinical translation. *Neural Regeneration Research, 21*, 1926 - 1946. https://doi.org/10.4103/nrr.nrr-d-24-01422