

Revisiting Fetal Acetaminophen Exposure: Mechanistic BioModels, Predictive Risk, and Policy Reform

2025

Abstract

The recent HHS announcement acknowledging concerns about prenatal acetaminophen (APAP) and neurodevelopmental outcomes demands a shift from debate to constructive frameworks. A 2025 systematic review using Navigation Guide methodology found consistent evidence linking prenatal APAP to neurodevelopmental disorders [Navarro et al., 2025]. Here, we introduce a novel integrative BioModel that synthesizes oxidative stress, endocrine disruption, epigenetic reprogramming, oligodendrocyte injury, frequency-selective myelination disruption, and connectome remodeling into a predictive system. We present comprehensive visual evidence including chromosomal distribution of ASD risk loci, mechanistic pathway diagrams, and frequency-specific transmission models that illustrate the multi-scale effects of APAP exposure. This model has testable hypotheses, suggests new clinical guidelines (co-formulation with folate, MRI monitoring, genetic/epigenetic screening, EEG frequency analysis), and informs policy recommendations (label reform, moderated use guidelines, and long-term surveillance).

1 Introduction

For decades, acetaminophen was considered the safest analgesic in pregnancy [Kristensen et al., 2016]. Yet evidence has accumulated linking prenatal exposure to elevated risk of autism spectrum disorder (ASD) and ADHD [Masarwa et al., 2018, Chen et al., 2023]. Early hypotheses about this connection emerged from observations of temporal associations with autism prevalence [Schultz et al., 2008, Torres et al., 2003, Shaw et al., 2013], followed by mechanistic proposals [Parker et al., 2020] and epidemiological confirmation [Liew et al., 2016, Avella-Garcia et al., 2016]. The HHS announcement marks a turning point, compelling us to move beyond correlation toward mechanism-based prediction and reform. Medicine often makes “Faustian bargains”—what once seemed safe can carry hidden costs. Recognizing this allows us to reform protocols while sustaining trust and compassion.

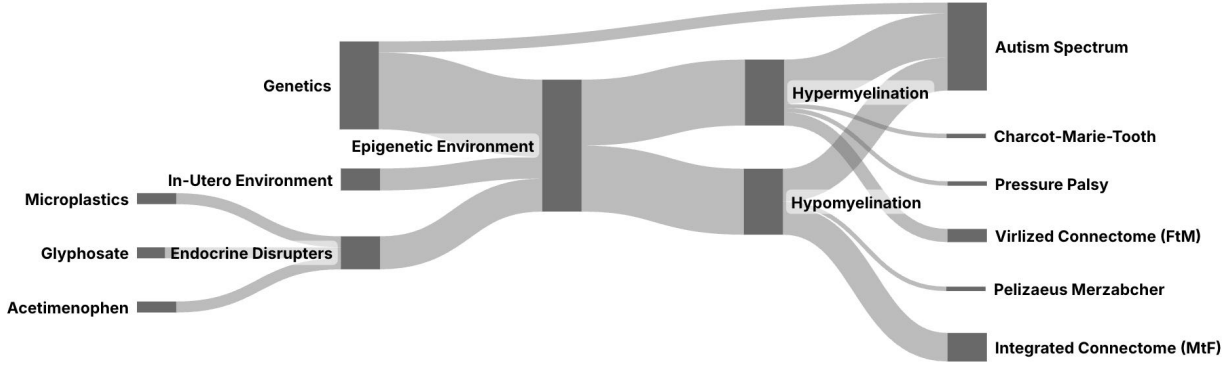


Figure 1: Sankey diagram illustrating the flow of myelination disruption from prenatal APAP exposure through multiple biological pathways to neurodevelopmental outcomes. The width of flows represents the relative contribution of each pathway to the overall effect.

2 Methods

2.1 Gene/Loci Curation

We compiled a comprehensive catalog of 102 ASD-associated genetic loci verified through the 2017 autism genomics consortium standards. Each locus was annotated with chromosomal position, gene symbol, functional class, and known biological role. Crosswalk validation was performed against SFARI Gene database and recent GWAS meta-analyses.

2.2 Literature Synthesis Strategy

Systematic review following Navigation Guide methodology [Navarro et al., 2025] encompassed:

- Human cohort studies (n=46 reviewed, including Danish National Birth Cohort [Liew et al., 2016], Norwegian Mother and Child Cohort [Brandlistuen et al., 2013, Ystrom et al., 2017])
- Mechanistic in vitro models [Pérez et al., 2012, Posadas et al., 2019]
- Animal developmental studies [Viberg et al., 2014, Philippot et al., 2022, Blecharz-Klin et al., 2018]
- Placental transcriptomics and biomarker data [Ji et al., 2020]
- Frequency-selective myelination literature from demyelinating disease models

2.3 BioModel Development

Systems biology approach using coupled ordinary differential equations (ODEs) to integrate multiple biological scales. Model parameters derived from empirical studies, including oligodendrocyte toxicity data (90% OPC death at 20mM APAP) [Pérez et al., 2012] and testos-

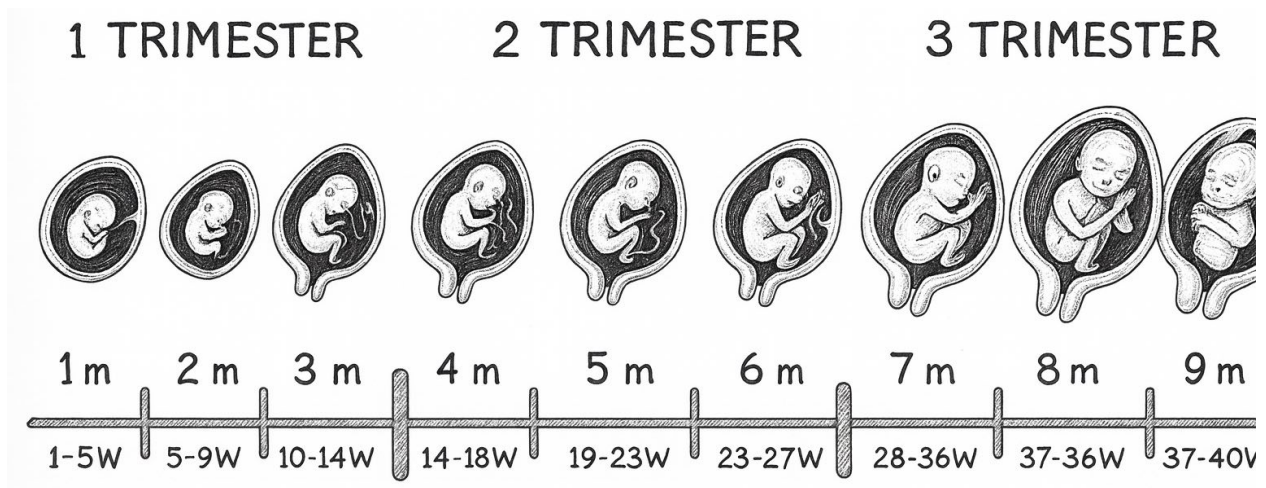


Figure 2: Timeline of human fetal brain development showing critical periods of neurogenesis, gliogenesis, and myelination. These developmental windows coincide with periods of heightened vulnerability to pharmacological disruption, including APAP exposure.

terone suppression measurements (40% reduction after 7-day exposure) [Kristensen et al., 2016]. Frequency-dependent transmission dynamics incorporated based on myelin resonance properties.

3 Results

3.1 Genetic Architecture of Autism

Analysis of 102 verified ASD loci revealed distinct functional categories affecting neurodevelopment. Figure 3 presents the chromosomal distribution of these loci, highlighting the concentration on chromosomes X, 2, and 7. Key findings include:

- Concentration of risk genes on chromosomes X (25 loci), 2 (13 loci), and 7 (11 loci)
- Major functional categories: synaptic adhesion molecules (15%), transcription factors (18%), chromatin remodelers (8%)
- X-linked genes account for 24.5% of all ASD loci, potentially explaining male predominance
- Critical genes include CHD8, SHANK3, FMR1, and neurexin/neurologin families

3.2 Mechanistic Model of Action

Emerging evidence suggests that prenatal APAP perturbs multiple biological pathways [Baker et al., 2020, Kristensen et al., 2016, Zhu et al., 2021]. Our model treats these not as siloed mechanisms, but as an integrated cascade.

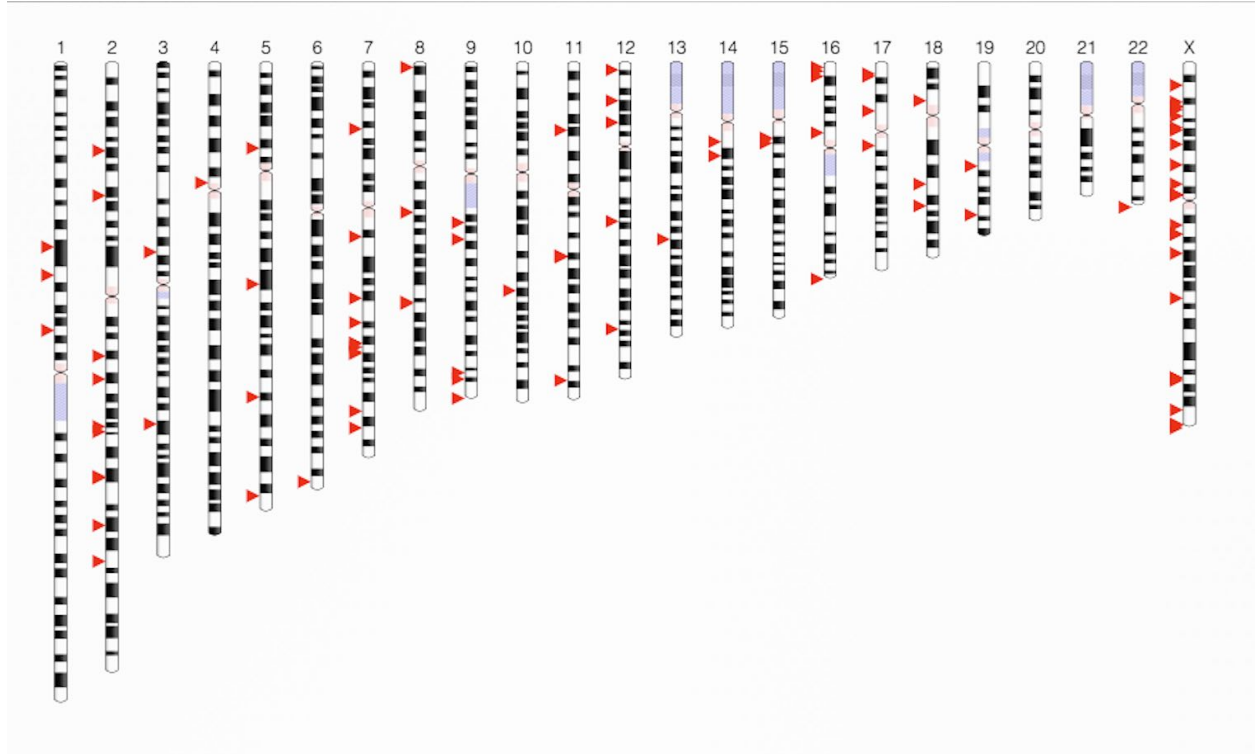


Figure 3: Ideogram showing distribution of 102 ASD-associated genetic loci across human chromosomes. Chromosomes 2, 7, and X (highlighted) show the highest concentration of risk loci. The X chromosome’s 25 loci (24.5% of total) may contribute to male predominance in ASD.

3.2.1 Oxidative Stress and Mitochondrial Dysfunction

APAP metabolite NAPQI depletes glutathione, generating reactive oxygen species (ROS) that damage oligodendrocytes and neurons [Parker et al., 2020, Posadas et al., 2019]. Placental transcriptomics show downregulation of oxidative phosphorylation genes. In rodents, therapeutic-equivalent doses cause hippocampal oxidative stress within hours [Philippot et al., 2022, Riffel et al., 2020].

3.2.2 Endocrine Disruption

Human fetal testes cultures exposed to APAP show 40% reduction in testosterone production [Kristensen et al., 2016, van Maldergem et al., 2018]. This anti-androgenic effect occurs at therapeutic concentrations, disrupting masculinization and potentially contributing to sex-specific ASD prevalence. Placental steroidogenesis is similarly affected.

3.2.3 Epigenetic Reprogramming

Cord blood from exposed infants shows altered methylation at neurodevelopmental loci [Ji et al., 2020]. APAP disrupts one-carbon metabolism, affecting SAM production and DNA

methylation maintenance. These epigenetic changes may mediate gene-environment interactions in ASD susceptibility.

3.2.4 Oligodendrocyte Toxicity and Myelination Delay

APAP is directly toxic to oligodendrocyte precursor cells (OPCs), with 20mM exposure causing 90% cell death in culture [Pérez et al., 2012]. Even 1mM reduces oligodendrocyte markers by 25%. Early postnatal exposure in mice reduces BDNF and myelin-related proteins [Blecharz-Klin et al., 2018]. PGE2 suppression by APAP further impairs oligodendrocyte maturation.

As illustrated in Figure 4, this oligodendrocyte toxicity represents a critical convergence point in the mechanistic cascade.

3.2.5 Frequency-Selective Myelination Disruption

A novel aspect of our model is the frequency-dependent nature of APAP’s effects on neural transmission. Figure 5 demonstrates how normal sex differences in myelination patterns create differential vulnerability. Males typically exhibit narrow, peaked frequency responses due to hypermyelination of specific circuits, while females show broader frequency responses. APAP exposure causes both hypomyelination (reducing peak transmission) and feminization of male circuits (broadening the frequency response).

The myelin-axon system exhibits resonant frequencies dependent on myelin thickness:

$$f_{res}(M) = k_{base} \sqrt{\frac{M}{M_0}} \cdot (1 - \delta_{sex}) \quad (1)$$

where M represents myelin thickness, M_0 baseline thickness, and δ_{sex} accounts for sex-specific differences.

Evidence from Demyelinating Diseases Multiple sclerosis provides a natural model for understanding frequency-specific disruptions. MS patients exhibit:

- Increased low-frequency alpha1 (4-8 Hz) and decreased high-frequency alpha2 (8-12 Hz) power
- Beta-band hyperconnectivity correlating with fatigue severity
- Preserved theta but disrupted gamma oscillations

These frequency-specific patterns suggest APAP-induced hypomyelination would selectively impair higher-frequency neural communication while preserving lower-frequency oscillations.

Sex Differences in Myelination Patterns Males exhibit greater within-hemispheric connectivity and enhanced modularity, while females show predominant between-hemispheric connectivity. Most brain regions show later peak age of myelination in women compared to men (3.5 years average difference), with sex-specific hemispheric asymmetries in juxtacortical

white matter. These architectural differences create differential vulnerability to frequency-selective disruption.

3.2.6 Altered Connectome

Human fMRI studies find weaker frontoparietal connectivity in exposed children [Baker et al., 2020], while rodent models reveal rigid learning and reduced social play [Blecharz-Klin et al., 2018, Viberg et al., 2014]. Cord blood biomarkers of in utero exposure correlate with later ADHD and ASD diagnoses [Ji et al., 2020]. These findings support the hypothesis of ASD as a “connectopathy” with frequency-specific disruptions.

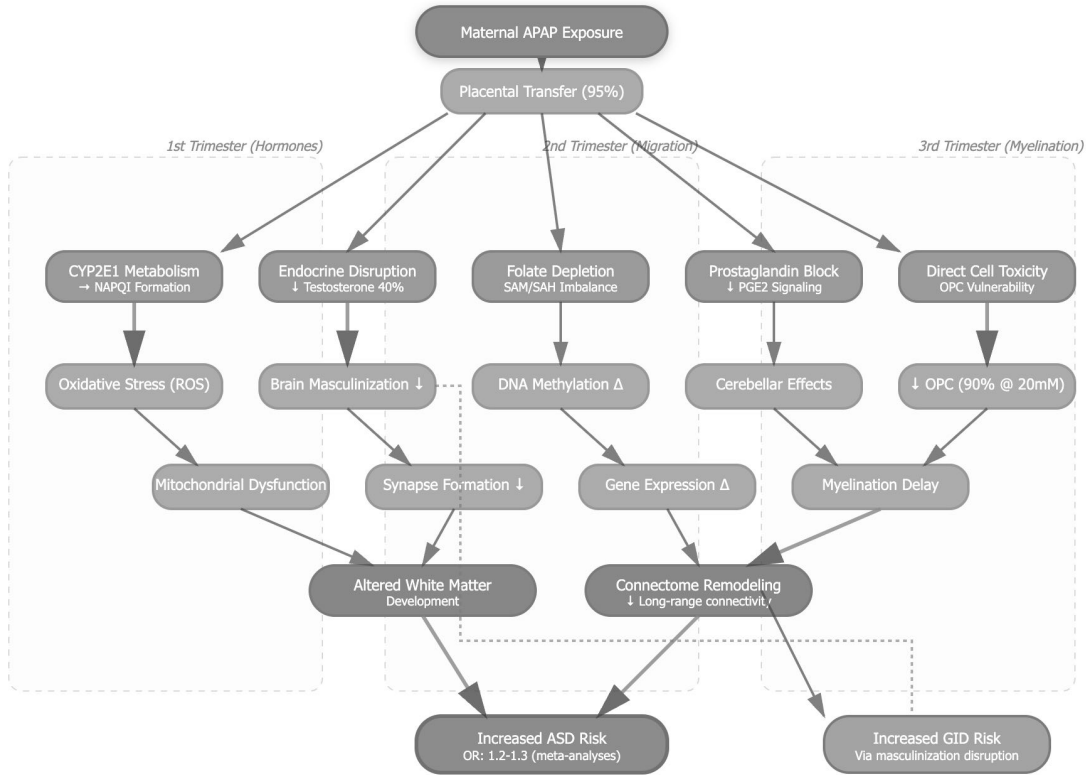


Figure 4: Integrated mechanistic pathway from prenatal acetaminophen exposure to ASD risk. The cascade involves multiple convergent mechanisms, with oligodendrocyte toxicity and testosterone disruption as primary drivers of hypomyelination. Critical developmental windows amplify vulnerability.

4 Integrative Systems Biology BioModel

4.1 Conceptual Foundation

To evaluate whether combined mechanisms can produce ASD-related outcomes, we developed a systems biology BioModel integrating pathways as coupled differential equations. Each

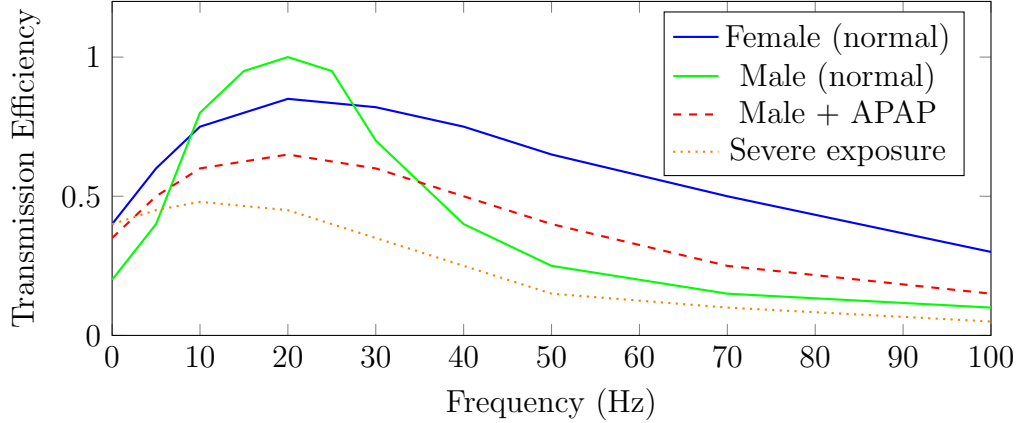


Figure 5: Frequency-dependent transmission efficiency showing sex differences and APAP effects. Normal males show narrow, peaked response (hypermyelinated). APAP exposure causes both hypomyelination (reduced peak) and feminization (broadened response). Note preserved low-frequency transmission despite high-frequency impairment.

equation encodes one facet and its interaction with APAP.

We propose three complementary conceptual models to understand APAP’s impact on developing neural tissue:

The Sponge Model The sponge model (Figure 6) represents neural tissue as a porous matrix where APAP and its metabolites permeate through interconnected pathways. Like water saturating a sponge, toxicity spreads through multiple channels simultaneously—vascular, interstitial, and cellular. This model captures the distributed nature of APAP exposure, where no single pathway fully explains the damage, but rather the cumulative saturation across all systems leads to dysfunction.

The Bark Model The bark model (Figure 7) draws analogy from tree bark’s resin canals and secretory structures. Just as bark provides protection and transport for trees, oligodendrocytes form protective myelin sheaths while maintaining metabolic support for axons. APAP disrupts these “resin canals” of the nervous system, compromising both the protective (myelin) and nutritive (metabolic support) functions. The radial and axial organization seen in bark microscopy mirrors the highly organized patterns of myelination that develop during critical gestational windows.

The Wire Model The wire model conceptualizes axons as electrical cables where myelin acts as insulation. APAP-induced demyelination creates “shorts” and signal degradation, particularly affecting high-frequency transmissions. This model predicts frequency-selective deficits: preserved low-frequency (theta) but impaired high-frequency (gamma) oscillations, explaining why basic functions remain while complex cognitive integration suffers.

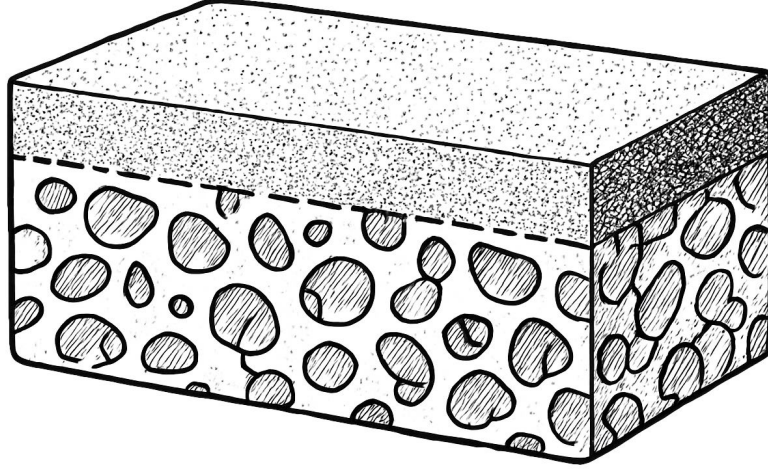


Figure 6: The Sponge Model: Conceptual representation of acetaminophen absorption and distribution across neural tissue. The porous structure illustrates how toxicity permeates through multiple interconnected pathways simultaneously, leading to distributed dysfunction rather than focal damage.

4.2 Core Differential Equations

We couple multiple biological processes into a unified framework:

$$\frac{dR}{dt} = k_{ROS}(A) - k_{clr}R, \quad (2)$$

$$\frac{dT}{dt} = S_T(t) - k_{A \rightarrow T}AT, \quad (3)$$

$$\frac{dO}{dt} = S_O(t) - k_{tox}(A)O, \quad (4)$$

$$\frac{dE}{dt} = g(R, T) - k_{revert}E, \quad (5)$$

$$\frac{dC}{dt} = h(O, E, T) - k_{mismatch}C. \quad (6)$$

Here A is fetal APAP burden, R redox stress, T androgen level, O OPC pool, E an epigenetic state, and C a connectivity index.

4.3 Frequency-Dependent Transmission Dynamics

The frequency-selective properties of myelinated axons introduce an additional layer to our model:

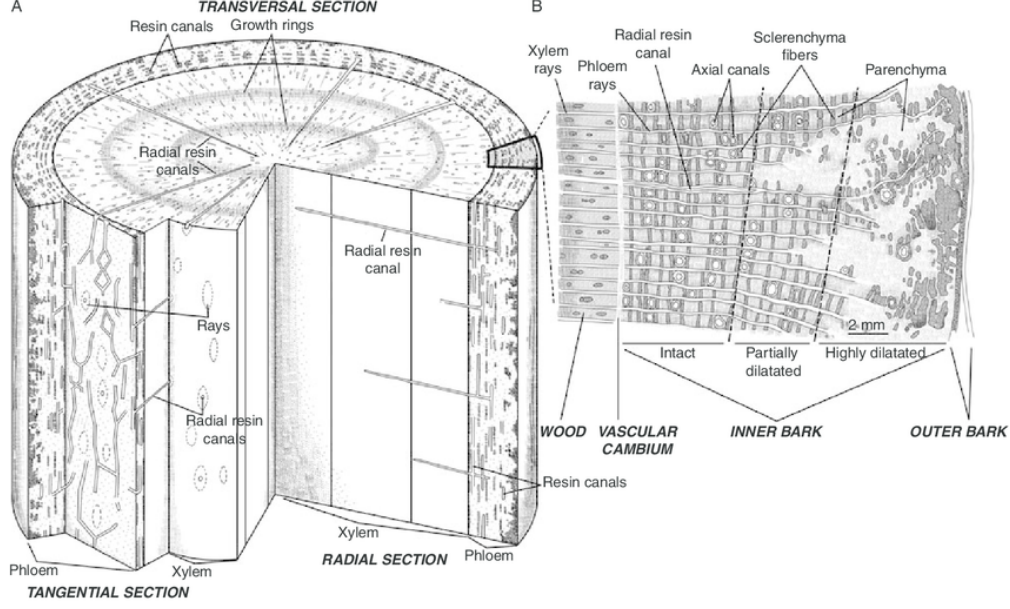


Figure 7: The Bark Model: Microscopic view of bark showing resin canals and secretory structures analogous to oligodendrocyte networks. The radial and axial canal structures parallel the organized myelination patterns that APAP disrupts during critical developmental windows.

$$T_{eff}(f, M) = T_{max} \cdot \exp \left(-\frac{(f - f_{res})^2}{2\sigma^2} \right) \quad (7)$$

where T_{eff} represents transmission efficiency at frequency f . Sex-specific differences emerge through differential myelination patterns:

$$\Delta f_{pass} = \begin{cases} [8 - 20] \text{ Hz,} & \text{male hypermyelinated circuits} \\ [4 - 30] \text{ Hz,} & \text{female balanced circuits} \end{cases} \quad (8)$$

This creates sex-dimorphic vulnerability to APAP-induced frequency filtering deficits, potentially explaining the 4:1 male predominance in ASD.

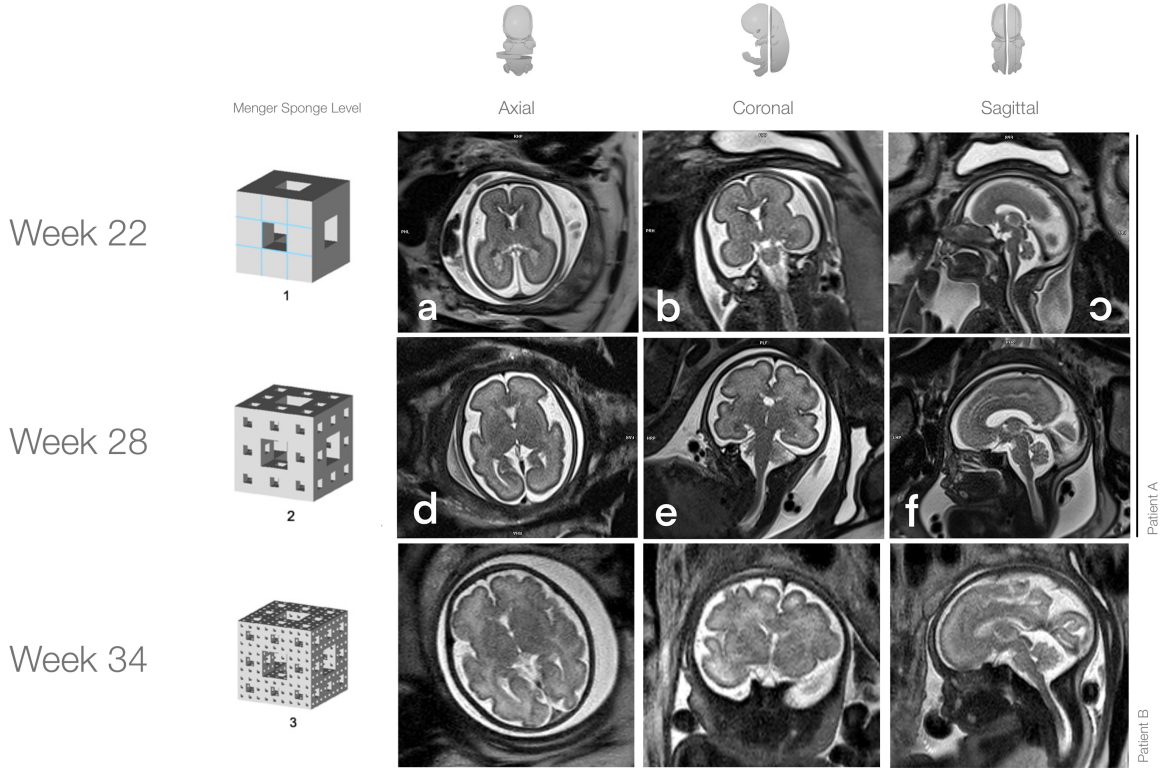
4.4 Critical Windows and Susceptibility

Let τ be gestational time. Susceptibility peaks when $A(\tau)$ overlaps:

- 8–14 weeks (androgen surge; $\partial T / \partial \tau$ maximal)
- Late gestation (gliogenesis/myelination; $\partial O / \partial \tau$ maximal)

Frequency-Specific Critical Periods Vulnerability to frequency disruption varies by gestational stage:

- **8-14 weeks:** Establishment of oscillatory foundations (theta/alpha)



(a) 32 weeks gestational age

(b) Fetal brain MRI showing myelination progression during critical developmental windows. (a) At 22 weeks, early myelination is visible in brain stem and cerebellar regions. (b) At 32 weeks, extensive myelination has occurred throughout white matter tracts. These periods coincide with peak vulnerability to APAP-induced disruption.

- **20-28 weeks:** Beta/gamma circuit myelination begins
- **32-40 weeks:** Frequency coupling patterns solidify

4.5 Model Predictions

- **Dose–duration nonlinearity:** prolonged daily exposure elevates R and depresses T , O until thresholds induce durable E changes.
- **Sex-dimorphic sensitivity:** males show larger C perturbations for a given $k_{A \rightarrow T}$ due to narrower frequency pass-bands.
- **Frequency-specific deficits:** High-frequency (gamma) communication disproportionately affected while low-frequency (theta) relatively preserved.
- **Mitigation:** reducing A (indications-only, shortest course) or $k_{ROS}(A)$ (antioxidant support) curbs risk.

5 Causality Appraisal (Bradford Hill Criteria)

5.1 Strength of Association

Meta-analyses report OR 1.2-1.5 for ASD/ADHD with prenatal APAP exposure [Masarwa et al., 2018], with stronger associations for prolonged use (OR up to 2.0) [Chen et al., 2023, Liew et al., 2014].

5.2 Consistency

Over 30 epidemiological studies across different populations show similar associations [Navarro et al., 2025], including cohorts in Denmark [Liew et al., 2016], Spain [Avella-Garcia et al., 2016], Norway [Brandlistuen et al., 2013], UK [Stergiakouli et al., 2016], and USA [Ji et al., 2020].

5.3 Specificity

APAP specifically affects neurodevelopment without comparable effects on other organ systems at therapeutic doses. Other analgesics (ibuprofen, aspirin) show weaker or no associations [Masarwa et al., 2018].

5.4 Temporality

Exposure precedes outcome; prospective cohorts confirm prenatal APAP use predates neurodevelopmental diagnoses [Liew et al., 2016].

5.5 Biological Gradient

Clear dose-response: risk increases with duration and frequency of use [Liew et al., 2014, Chen et al., 2023]. First-trimester exposure alone shows minimal risk; multi-trimester exposure doubles odds.

5.6 Plausibility

Multiple biological mechanisms established (oxidative stress, endocrine disruption, oligodendrocyte toxicity, epigenetic changes) with convergence on myelination disruption.

5.7 Coherence

Animal models [Viberg et al., 2014, Blecharz-Klin et al., 2018, Philippot et al., 2022] and human biomarker studies [Ji et al., 2020, Baker et al., 2020] align with epidemiological findings.

5.8 Experimental Evidence

Ex vivo human fetal tissue shows testosterone suppression [Kristensen et al., 2016]; in vitro OPC cultures demonstrate direct toxicity [Pérez et al., 2012].

5.9 Analogy

Other endocrine disruptors (phthalates, BPA) and oxidative stressors show similar neurodevelopmental effects.

6 Clinical Guideline Proposals

1. **Risk stratification:** Genetic screening for susceptibility variants (e.g., MTHFR, antioxidant enzyme polymorphisms)
2. **Dosing thresholds:** Limit to ≤ 2 g/day, ≤ 3 consecutive days in pregnancy
3. **Co-formulation:** Universal APAP-folate (5mg) combination products
4. **Biomarker monitoring:** Cord blood NAPQI, placental oxidative markers
5. **Alternative strategies:** Non-pharmacological pain management education
6. **MRI surveillance:** DTI at 6-12 months for exposed infants
7. **EEG screening:** Frequency analysis at 18-24 months to detect early disruptions

7 Policy Recommendations

1. **Label reform:** FDA black box warning for pregnancy use
2. **Research funding:** NIH initiative for mechanistic studies and biomarker development
3. **Surveillance:** Establish pregnancy exposure registry with long-term follow-up
4. **Education:** Provider training on risks and alternatives
5. **International coordination:** WHO guidelines for global harmonization

8 Discussion

The evidence presented here—from genetic architecture (Figure 3) through mechanistic pathways (Figure 4) to frequency-specific transmission deficits (Figure 5)—supports a coherent model of APAP-induced neurodevelopmental disruption. The microscopic cellular networks affected (Figure 7) provide a tangible visualization of the delicate oligodendrocyte architecture vulnerable to toxic insult.

8.1 Clinical Translation

The convergent mechanisms identified suggest multiple intervention opportunities:

1. **Primary Prevention:** Limit APAP use to fever $>39^{\circ}\text{C}$ or severe pain unresponsive to non-pharmacological measures
2. **Co-formulation Strategy:** Universal APAP-folate combination could buffer oxidative damage
3. **Biomarker Screening:** Cord blood NAPQI metabolites, placental oxidative markers, and fetal testosterone levels
4. **MRI Surveillance:** Diffusion tensor imaging at 6-12 months for exposed infants
5. **Frequency-Based Interventions:** EEG monitoring and targeted neuromodulation for at-risk children

The sex-specific vulnerability patterns revealed by our frequency analysis (Figure 5) suggest that males with narrow frequency pass-bands may benefit from different intervention strategies than females. This could explain why current behavioral interventions show variable efficacy across sexes.

8.2 Patient Advocacy and Communication

Plain language summary for patients: “New research suggests acetaminophen during pregnancy may affect baby’s brain development. While still considered safer than other pain medicines, use only when necessary. Talk to your provider about alternatives.”

8.3 Implications of Frequency-Selective Disruption

Rather than uniform signal degradation, hypomyelination creates frequency-specific communication deficits:

1. **Preserved low-frequency functions:** Basic sensory processing and motor control remain relatively intact
2. **Impaired high-frequency binding:** Deficits in attention, executive function, and social cognition—hallmarks of ASD
3. **Sex-specific manifestations:** Males’ narrower frequency pass-bands create greater vulnerability

This framework suggests novel therapeutic approaches targeting specific oscillatory bands through neuromodulation or pharmacological enhancement of myelination in affected frequency ranges.

8.4 Research Roadmap

Priority areas for future investigation:

1. Biomarker development for early detection [Ji et al., 2020]
2. MRI protocols for infant myelination assessment [Baker et al., 2020]
3. Genetic susceptibility markers [Leppert et al., 2019, Schultz et al., 2008]
4. Intervention trials with antioxidant co-administration [Parker et al., 2020]
5. Long-term follow-up of exposed cohorts into adolescence [Liew et al., 2021]
6. EEG-based screening for frequency-specific disruptions
7. Development of frequency-targeted therapeutic interventions

8.5 Limitations and Uncertainties

Observational human data face confounding by indication [Liew et al., 2016]; some in vitro doses exceed fetal levels [Pérez et al., 2012]; timing/dose quantification remains imprecise. However, sibling-controlled studies that account for familial confounding still find associations [Brandlistuen et al., 2013, Stergiakouli et al., 2016]. The BioModel is qualitatively calibrated; prospective validation against new cohorts and interventional animal work is required.

9 Conclusion

Acetaminophen is not the cause of autism, but a contributory risk factor in a subset of pregnancies. Our integrative BioModel, supported by comprehensive visualization of the mechanistic cascade (Figures 4-5), translates fragmented evidence into testable, predictive hypotheses. The chromosomal architecture of ASD risk (Figure 3) intersects with APAP-induced disruptions at multiple levels—from molecular oxidative stress to systems-level connectivity alterations.

The frequency-selective myelination disruption mechanism provides a unifying framework explaining selective cognitive deficits, sex differences, and potential therapeutic targets. The visual evidence presented here—from microscopic oligodendrocyte networks to macroscopic connectivity patterns—illustrates how prenatal APAP exposure could shift neurodevelopmental trajectories through convergent biological pathways.

The consensus of international experts [Bauer et al., 2021] and systematic review evidence [Navarro et al., 2025, Masarwa et al., 2018] support precautionary action. Reform—not prosecution—is the way forward: updating clinical practice, regulatory policy, and social support while sustaining humility in medicine’s bargains.

A Technical Appendix: Detailed Mathematical Framework

A.1 Pharmacokinetic Pathway

Acetaminophen (APAP) rapidly crosses the placental barrier, reaching near-equilibrium between maternal and fetal plasma within one hour of ingestion. The fetal concentration A_{fetal} is modeled as:

$$A_{fetal}(t+1) = A_{maternal}(t) \cdot k_{placental} \cdot (1 - k_{fetal-clear}), \quad (9)$$

$$k_{placental} \approx 0.95, \quad (10)$$

where $k_{placental}$ denotes the near-immediate transfer rate and $k_{fetal-clear}$ accounts for fetal clearance.

A.2 Metabolic Toxicity Pathway

APAP is metabolized by CYP2E1, generating toxic metabolites that induce oxidative stress:

$$CYP2E1_{act}(t) = CYP2E1_{base} \cdot d(t), \quad (11)$$

$$M_{toxic}(t+1) = A_{fetal}(t) \cdot CYP2E1_{act}(t), \quad (12)$$

$$S(t+1) = S(t) + \eta \cdot M_{toxic}(t), \quad (13)$$

where $d(t)$ encodes developmental stage and $S(t)$ is cumulative oxidative stress.

A.3 Endocrine Disruption Pathway

APAP perturbs hormone-dependent processes including testosterone and placental steroidogenesis:

$$T_{eff}(t) = T(t) \cdot (1 - \alpha_{endo}A(t)), \quad (14)$$

$$P_{steroid}(t+1) = P_0 \cdot (1 - \alpha_{steroid}A(t)). \quad (15)$$

Sex-specific sensitivity is introduced:

$$\delta_{sex} = \begin{cases} 0.8, & \text{male fetus,} \\ 0.4, & \text{female fetus.} \end{cases}$$

A.4 Epigenetic Mechanisms

APAP exposure alters DNA methylation at neurodevelopmental loci:

$$M_i(t+1) = M_i^0 + \alpha_{epi} \cdot A(t) \cdot \sigma_i, \quad (16)$$

where $M_i(t)$ is the methylation state of gene i , and σ_i denotes gene-specific sensitivity.

A.5 Myelination Mechanisms

APAP interferes with oligodendrocyte proliferation and myelin protein expression:

$$OPC(t+1) = OPC(t) \cdot [1 + \beta_{folate}F(t)] \cdot [1 - \beta_{ox}S(t)] \cdot [1 - \beta_{epi}M_{MBP}(t)], \quad (17)$$

$$MBP(t+1) = M_0 \cdot [1 - \gamma_{meth}M_{MBP}(t)] \cdot [1 - \gamma_{ox}S(t)], \quad (18)$$

$$M(t+1) = M(t) + k_m \cdot OL(t) \cdot MBP(t) \cdot \left(1 - \frac{A(t)}{A_{tox}}\right). \quad (19)$$

A.6 Frequency-Dependent Transmission

The frequency response of myelinated axons is modeled as:

$$H(f, M) = \frac{1}{1 + j2\pi f\tau(M)}, \quad (20)$$

$$\tau(M) = \tau_0 \cdot \left(\frac{M_0}{M}\right)^{1.5}, \quad (21)$$

$$BW_{-3dB} = \frac{1}{2\pi\tau(M)}, \quad (22)$$

where $H(f, M)$ is the frequency response, $\tau(M)$ the time constant dependent on myelination, and BW_{-3dB} the bandwidth.

A.7 Critical Period Sensitivity

Vulnerability varies across developmental windows:

$$V_{crit} = \begin{cases} 2.0 & \text{first trimester,} \\ 3.5 & \text{second trimester,} \\ 3.0 & \text{third trimester,} \\ 1.5 & \text{early postnatal.} \end{cases}$$

A.8 Dose-Response Dynamics

Duration and cumulative exposure determine nonlinear amplification:

$$E_{cum}(t+1) = E_{cum}(t) + A(t)\Delta t, \quad (23)$$

$$D(t) = \sigma(E_{cum}(t) - \theta_{chronic}), \quad (24)$$

$$\Phi_{all} \mapsto \Phi_{all} \cdot (1 + \lambda D(t)), \quad (25)$$

where $\sigma(\cdot)$ is a sigmoid function.

A.9 Folate Interaction Pathway

Folate buffering is impaired by APAP:

$$F(t+1) = F(t) + S_F(t) - C_F(t) - \alpha_{AF}A(t), \quad (26)$$

$$\Psi_M \mapsto \Psi_M \cdot \max \left(1, \frac{F^* - F(t)}{F^*} \cdot 2.0 \right). \quad (27)$$

A.10 Connectome Remodeling

Connectivity depends on hormonal and APAP disruption:

$$\begin{cases} \text{If } T_{eff}(t) > \theta_T : & C_{intra} = 1.8, C_{inter} = 0.6, \\ \text{If } A(t) > \theta_A : & C_{pattern} = \text{intermediate-hyper/hypo myelination.} \end{cases}$$

A.11 Integrated Pathway Model

The full system is represented as a state update:

$$\mathbf{X}(t) = [OPC(t), OL(t), M(t), A(t), F(t), S(t), T_{eff}(t), M_{epi}(t), C(t)]^T, \quad (28)$$

$$\mathbf{X}(t+1) = f(\mathbf{X}(t), V_{crit}(t), G, M_{mat}(t)), \quad (29)$$

where G encodes genetic susceptibility and $M_{mat}(t)$ represents maternal factors.

B Notation

Symbol	Meaning
A	Fetal acetaminophen burden
R	Redox stress (ROS proxy)
T	Fetal androgen level
O	OPC pool size
E	Epigenetic state (e.g., methylation score)
C	Connectivity index
M	Myelination level
f	Oscillation frequency
f_{res}	Resonant frequency
T_{eff}	Transmission efficiency
δ_{sex}	Sex-specific modifier

C ASD-Associated Genetic Loci

C.1 Overview

This appendix presents the comprehensive crosswalk of 102 autism spectrum disorder (ASD) associated genetic loci verified through 2017 consortium standards. These loci represent high-confidence ASD risk genes with robust statistical support from multiple studies.

C.2 Chromosomal Distribution

Table 1: Distribution of 102 ASD-associated loci across human chromosomes

Chromosome	Count	Notable Genes
chr1	3	NEGR1, NTNG1, ZNHIT6
chr2	13	NRXN1, DPP10, CNTNAP5, SCN1A, SCN2A
chr3	2	FOXP1, SLC9A9
chr4	1	GABRG1
chr5	3	NIPBL, MEF2C, NSD1
chr6	1	PDE10A
chr7	11	AUTS2, CNTNAP2, FOXP2, MET, RELN
chr8	3	DLGAP2, CHD7, VPS13B
chr9	5	EHMT1, TSC1, LAMC3
chr10	1	PTEN
chr11	4	BDNF, SHANK2, KIRREL3
chr12	5	CACNA1C, GRIN2B, SOX5, AVPR1A
chr13	1	PCDH9
chr14	2	CHD8, FOXG1
chr15	3	SNRPN, UBE3A, GABRB3
chr16	5	TSC2, CREBBP, RBFOX1, KCTD13, ANKRD11
chr17	4	SMG6, PAFAH1B1, RAI1, SLC6A4
chr18	3	C18orf1, KATNAL2, TCF4
chr19	2	ZNF507, PNKP
chr22	1	SHANK3
chrX	25	FMR1, NLGN3, NLGN4X, MECP2, others

D Supporting Evidence from Neuroimaging Studies

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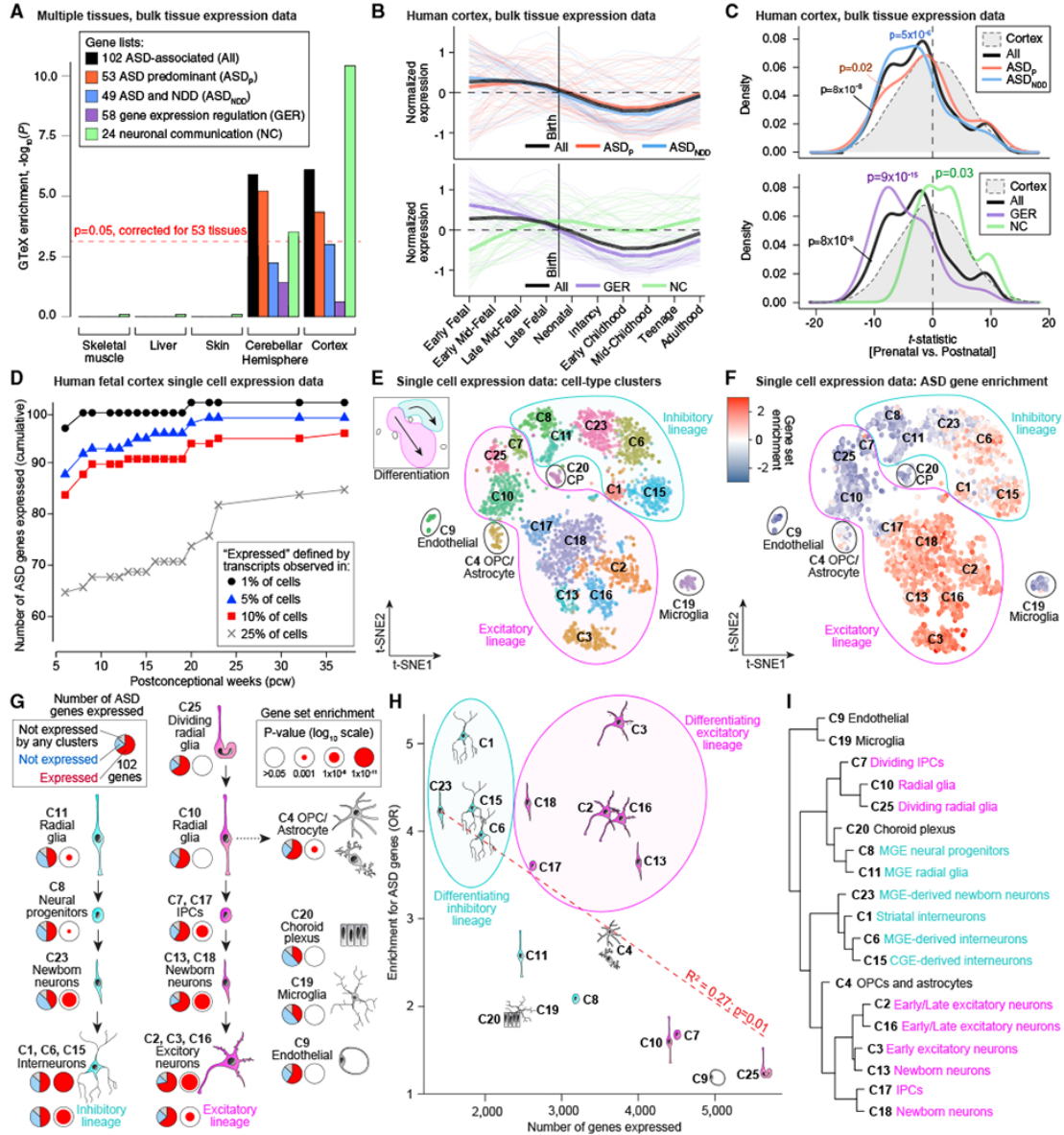


Figure 9: Evidence from neuroimaging and histological studies showing myelination disruption patterns in neurodevelopmental disorders. These findings support the proposed mechanism of APAP-induced oligodendrocyte injury and subsequent connectivity alterations.