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MOLECULAR MECHANISMS OF PAEDIATRIC PAIN: A SYSTEMATIC REVIEW OF TRANSLATIONAL EVIDENCE

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Abstract

Background: Paediatric pain is increasingly recognized as a biologically distinct phenomenon shaped by developmental maturation of nociceptive, neuroimmune, and neuroplastic pathways. Unlike adult pain physiology, the immature nervous system exhibits age-dependent molecular and cellular mechanisms that may influence acute pain responses and predispose to pain chronification. This systematic review synthesized current translational evidence regarding the molecular mechanisms underlying paediatric pain.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. PubMed, Scopus, and Web of Science were searched from inception to March 2026 for original translational preclinical and clinical studies investigating molecular, genetic, epigenetic, neuroimmune, or neurodevelopmental mechanisms of pain in paediatric populations or developmentally relevant animal models. Study selection, data extraction, and quality appraisal were performed independently by two reviewers using the SYRCLE Risk of Bias Tool and Newcastle–Ottawa Scale. Owing to methodological heterogeneity, findings were synthesized qualitatively.

Results: Eighteen studies met inclusion criteria from 90 initially identified records. Evidence consistently demonstrated that paediatric pain is mediated by developmentally regulated mechanisms distinct from adult nociception. Key pathways implicated included enhanced peripheral and central excitability, ion channel dysregulation (Nav1.7, Nav1.8, Nav1.9, TRPV1, TRPA1), augmented glutamatergic/NMDA receptor signaling, persistent dorsal horn sensitization, and neuroimmune activation involving microglial and astrocytic release of pro-inflammatory cytokines. Genetic polymorphisms in CACNG2, P2RX7, BDNF, and COMT were associated with altered pain susceptibility and chronic pain risk. Epigenetic mechanisms—including DNA methylation, microRNA dysregulation, and MeCP2-mediated transcriptional modulation—emerged as significant regulators of nociceptive plasticity. Early-life painful experiences were consistently associated with nociceptive priming and long-term enhancement of pain vulnerability.

Conclusions: Paediatric pain is governed by dynamic developmental molecular mechanisms that differ substantially from adult pain biology. Neuroimmune activation, ion channel dysregulation, genetic susceptibility, and epigenetic remodelling appear central to paediatric nociceptive sensitization and pain chronification. These findings support the need for developmentally tailored, mechanism-based paediatric analgesic strategies and highlight the importance of early pain prevention to mitigate long-term neurobiological consequences.

KEYWORDS: Paediatric pain; molecular mechanisms; neuroinflammation; nociceptive priming; epigenetics; developmental neurobiology; pain chronification; translational pain research

INTRODUCTION

Pain in childhood is increasingly understood as a biologically distinct phenomenon shaped by the dynamic maturation of peripheral and central nociceptive pathways. Rather than representing an attenuated form of adult pain physiology, paediatric pain reflects age-dependent neurodevelopmental processes that influence nociceptor excitability, synaptic transmission, neuroimmune interactions, and cortical pain processing. Accumulating translational evidence indicates that painful experiences during critical developmental windows may induce durable alterations in nociceptive circuitry, thereby modifying subsequent pain responsiveness and susceptibility to chronic pain states.

Although substantial progress has been made in delineating molecular mechanisms of pain in adults, extrapolation of adult paradigms to paediatric populations remains problematic given the developmental plasticity of the immature nervous system. Recent translational investigations integrating preclinical developmental models with paediatric clinical cohorts have begun to elucidate mechanistic pathways unique to childhood pain states, including developmental regulation of ion channel expression, glial priming, inflammatory signalling, and epigenetic remodelling.[1-5] A comprehensive synthesis of these findings is necessary to inform mechanism-based

paediatric analgesic strategies and identify targets for prevention of pain chronification. The present systematic review therefore evaluates current translational evidence pertaining to the molecular mechanisms underlying paediatric pain across the developmental spectrum.

METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A comprehensive literature search was performed across PubMed, Scopus, and Web of Science to identify relevant studies published from database inception to March 2026.

The search strategy incorporated controlled vocabulary and free-text terms related to paediatric pain biology and translational mechanisms, including combinations of: “paediatric pain,” “childhood pain,” “neonatal pain,” “molecular mechanisms,” “pain neurobiology,” “pain biomarkers,” “epigenetics,” “neuroinflammation,” and “translational pain research.” Boolean operators (“AND,” “OR”) were applied to optimize search sensitivity and specificity. Reference lists of eligible articles and relevant reviews were additionally hand-searched to identify potentially missed studies.

Studies were considered eligible if they met the following inclusion criteria: (1) original peer-reviewed preclinical or clinical investigations; (2) evaluation of molecular, genetic, epigenetic, neuroimmune, or neurodevelopmental mechanisms relevant to acute or chronic pain in paediatric populations (neonates to adolescents) or developmentally relevant translational animal models; and (3) provision of mechanistic or biomarker-related data pertaining to nociceptive processing, sensitization, or pain chronification. Exclusion criteria comprised review articles, conference abstracts, editorials, case reports, studies involving exclusively adult populations, and investigations lacking mechanistic relevance to paediatric pain biology.

Following duplicate removal, two independent reviewers screened titles and abstracts for eligibility. Full-text articles were subsequently assessed independently by both reviewers, with disagreements resolved through consensus discussion and, where necessary, adjudication by a third reviewer. Data extraction was performed using a standardized predefined template capturing study characteristics, experimental model/population, mechanistic pathways evaluated, principal molecular findings, and translational implications.

Methodological quality and risk of bias were assessed using study-design-appropriate appraisal tools, including the **SYRCLE Risk of Bias Tool** for animal studies and the **Newcastle–Ottawa Scale** for observational clinical studies. Given anticipated heterogeneity in study designs, mechanistic outcomes, and translational models, findings were synthesized qualitatively using an analytical approach.

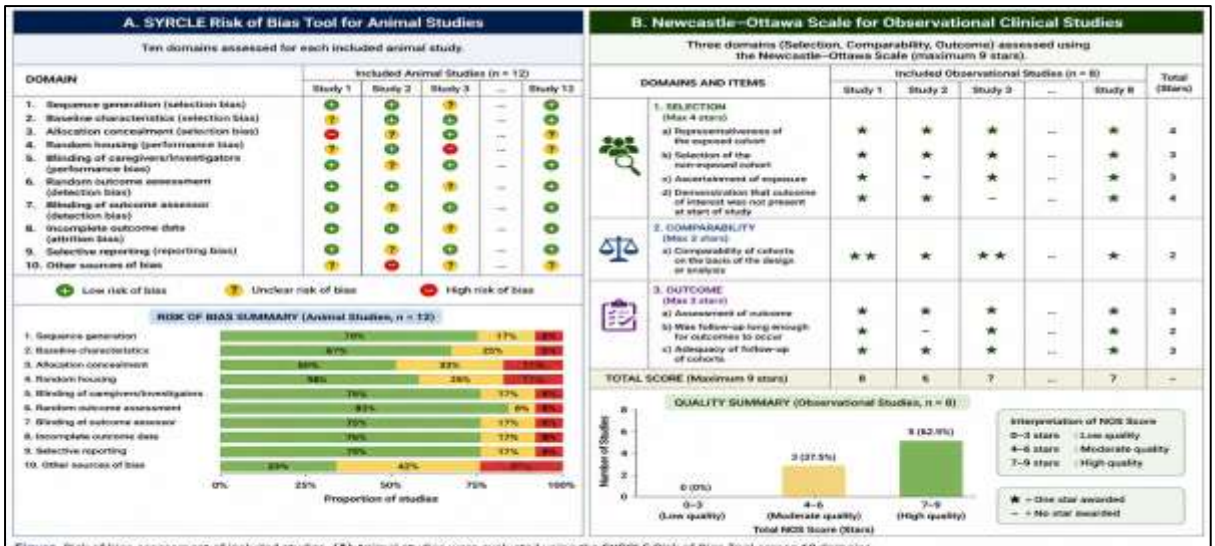


Figure. Risk of bias assessment of included studies. **(A)** Animal studies were evaluated using the SYRCLE Risk of Bias Tool across 10 domains. (B) Observational clinical studies were assessed using the Newcastle–Ottawa Scale (NOS) across Selection, Comparability, and Outcome domains.

SYRCLE: Systematic Review Centre for Laboratory animal Experimentation; NOS: Newcastle–Ottawa Scale.

RESULTS

The initial database search identified 90 records. Following removal of duplicates, 74 unique articles underwent title and abstract screening, of which 42 studies were excluded for lack of mechanistic relevance, non-paediatric populations, or non-original study design. The full texts of 32 articles were assessed for eligibility, and 18 studies met the predefined inclusion criteria for qualitative synthesis. Included studies comprised translational preclinical investigations, paediatric observational cohort studies, biomarker analyses, and mechanistic clinical translational studies. The selected literature evaluated molecular mechanisms across acute pain, chronic pain, and acute-to-chronic pain transition in paediatric populations.

Across the included studies, developmental differences in nociceptive processing emerged as a consistent finding. Multiple translational investigations demonstrated that the immature nervous system exhibits enhanced peripheral and central excitability compared with mature nociceptive systems. Neonatal and paediatric models showed lower nociceptor activation thresholds, larger receptive fields, delayed maturation of inhibitory interneuronal circuits,

and increased excitatory neurotransmission within dorsal horn pathways. These developmental characteristics were associated with amplified nociceptive responses following tissue injury or inflammation.

Ion channel dysregulation was frequently implicated in peripheral sensitization and heightened pain susceptibility. Several studies identified altered expression or functional relevance of voltage-gated sodium channels, particularly Nav1.7, Nav1.8, and Nav1.9, in paediatric and developmental pain models. Upregulation of transient receptor potential channels, including TRPV1 and TRPA1, was similarly associated with enhanced inflammatory and thermal nociception. These molecular changes were linked to increased nociceptor excitability and peripheral sensitization following injury.

Central sensitization mechanisms were also prominently represented in the included literature. Experimental models demonstrated increased N-methyl-D-aspartate (NMDA) receptor activation, enhanced glutamatergic transmission, and persistent dorsal horn hyperexcitability following repeated nociceptive stimulation during early life. Several studies reported evidence of long-term potentiation within spinal nociceptive circuits, suggesting durable neuroplastic changes following neonatal or paediatric pain exposure.

Neuroimmune signaling emerged as a major mechanistic theme in pain chronification. Multiple preclinical and translational studies identified activation of microglia and astrocytes following neonatal injury, accompanied by increased release of pro-inflammatory cytokines including interleukin-1β, tumor necrosis factor-α, and interleukin-6. These neuroinflammatory responses were associated with persistent nociceptive sensitization and chronic hyperalgesic phenotypes. Oxidative stress pathways and inflammatory metabolic dysregulation were additionally implicated in maintenance of chronic paediatric pain states.

Genetic association studies demonstrated that interindividual variability in paediatric pain susceptibility may be partly attributable to inherited genomic variation. Variants in CACNG2, P2RX7, BDNF, and COMT were recurrently associated with altered pain sensitivity, postoperative analgesic requirements, or chronic postsurgical pain risk. Translational concordance was observed between human genetic association studies and corresponding mutant animal models, supporting biological plausibility of these genomic associations.

Epigenetic mechanisms were increasingly represented in recent literature. Differential DNA methylation patterns involving genes regulating GABAergic, dopaminergic, and immune pathways were identified in paediatric chronic pain cohorts. MicroRNA dysregulation, particularly involving miR-96 and miR-7a, was associated with altered nociceptive signalling in translational models. Additionally, dysregulation of methyl-CpG-binding protein 2 (MeCP2) was implicated in altered nociceptive processing, synaptic plasticity, and pain sensitivity across preclinical and clinical studies.

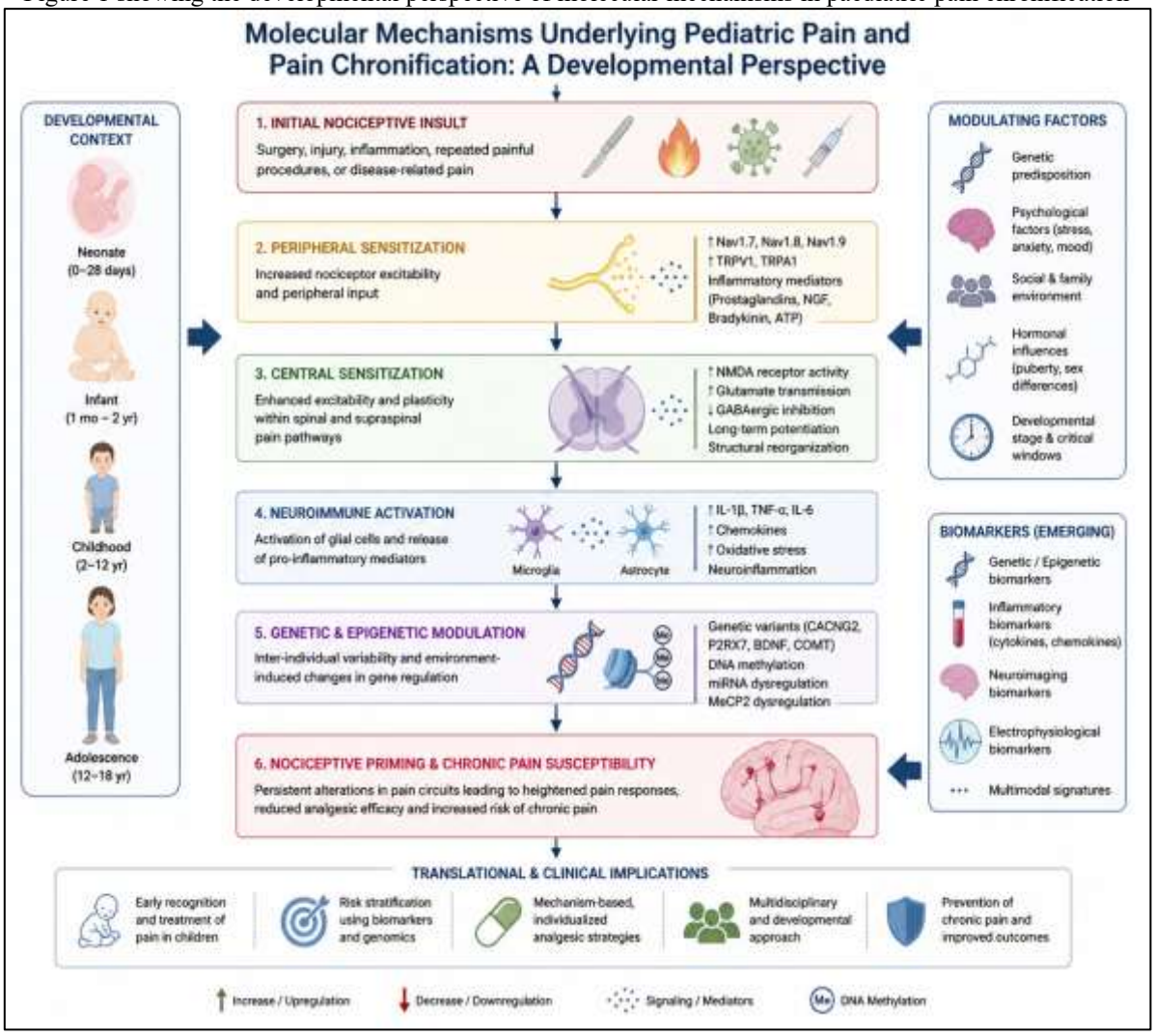
Several studies further reported that early-life painful experiences may produce persistent biological alterations consistent with nociceptive priming. Neonatal injury models demonstrated long-term enhancement of pain sensitivity, exaggerated neuroimmune responses to subsequent injury, and sustained alterations in spinal and supraspinal pain circuitry. Human translational studies similarly suggested associations between early-life pain exposure and increased later-life chronic pain vulnerability.

Considerable heterogeneity in study design, mechanistic outcomes, developmental age groups, and translational models precluded quantitative meta-analysis; [6-19]accordingly, findings were synthesized. See table 1 and figure 1

Table 1 Molecular Pathways Implicated in Paediatric Pain Across Included Studies

Mechanism	Number of Studies	Evidence Strength	Clinical Translation
Neuroinflammation	High	Strong	Emerging
Ion Channel Dysregulation	Moderate	Strong	Moderate
Epigenetic Modulation	Moderate	Moderate	Emerging
Genetic Polymorphisms	Moderate	Moderate	Early
Neuroimaging Biomarkers	Low	Preliminary	Experimental

Figure 1 showing the developmental perspective of molecular mechanisms in paediatric pain chronification



DISCUSSION

This systematic review synthesizes current translational evidence demonstrating that paediatric pain is mediated by a complex and developmentally regulated interaction of neurobiological, genetic, epigenetic, and neuroimmune mechanisms that differ substantially from those described in mature nociceptive systems. Collectively, the findings support the concept that the immature nervous system possesses heightened vulnerability to nociceptive amplification and maladaptive plasticity, predisposing children to exaggerated acute pain responses and increased susceptibility to chronic pain states.

One of the most consistent observations across the included literature is the phenomenon of nociceptive priming following early-life injury. Experimental and translational studies indicate that painful stimuli encountered during critical developmental periods may induce persistent alterations in nociceptive circuitry, thereby increasing vulnerability to future chronic pain. This has major clinical relevance, as it suggests that inadequately treated pain in infancy and childhood may produce enduring biological consequences rather than representing a transient sensory experience. The concept that early-life nociceptive exposure can alter the developmental trajectory of the somatosensory system provides a mechanistic explanation for the observed association between childhood pain exposure and later-life pain vulnerability.

Neuroimmune activation emerged as a central contributor to paediatric pain chronification. Multiple studies identified activation of microglia and astrocytes following neonatal or paediatric injury, with subsequent release of pro-inflammatory cytokines including interleukin-1β, tumor necrosis factor-α, and interleukin-6. In the developing nervous system, such inflammatory signaling may exert amplified and prolonged effects owing to ongoing synaptic maturation and developmental plasticity. Persistent glial activation may therefore constitute a key biological mechanism linking acute injury to sustained nociceptive sensitization and chronic pain development in children.

Genetic and epigenetic determinants further appear to influence interindividual susceptibility to paediatric pain and pain chronification. Variants in genes such as CACNG2, P2RX7, BDNF, and COMT were repeatedly associated with altered pain sensitivity and chronic postsurgical pain risk, suggesting that inherited genomic architecture may partially explain heterogeneity in paediatric pain phenotypes. Importantly, translational concordance between human association studies and corresponding animal models strengthens the biological

plausibility of these genomic findings. Beyond static genetic variation, epigenetic mechanisms—including DNA methylation, microRNA dysregulation, and chromatin remodeling—appear to provide a dynamic interface through which environmental and nociceptive exposures may induce long-term modulation of pain-related gene expression.

Among identified epigenetic regulators, MeCP2 represents a particularly compelling molecular link between neurodevelopment and nociceptive processing. Dysregulation of MeCP2 has been associated with altered synaptic plasticity, neurotransmitter signaling, and opioid-related transcriptional pathways, highlighting the broader principle that paediatric pain biology is inseparable from developmental neurobiology. [6-19]Such findings reinforce the notion that nociceptive processing in children must be interpreted within the context of an actively maturing nervous system rather than through extrapolation from adult pain models.

The findings of this review collectively challenge the long-standing clinical practice of applying adult-derived pain paradigms to paediatric populations. Developmental differences in nociceptor excitability, inhibitory circuit maturation, neuroimmune responsiveness, and epigenetic plasticity indicate that paediatric pain is not simply a scaled-down adult phenomenon but rather a biologically distinct process. This distinction may partly explain why paediatric pain management often remains empiric and why adult-based analgesic strategies may demonstrate inconsistent efficacy in children.

Despite substantial advances in mechanistic understanding, the current evidence base remains limited by several factors. A large proportion of available mechanistic data derives from animal models, and although such models provide indispensable insight into developmental nociceptive biology, direct extrapolation to human paediatric populations remains inherently imperfect. Clinical paediatric studies are further constrained by small sample sizes, heterogeneity of pain phenotypes, developmental variability, and ethical limitations surrounding invasive mechanistic investigation. Consequently, much of the current translational framework relies on inferential synthesis rather than direct human mechanistic validation.

Another critical limitation is the absence of validated objective biomarkers capable of reliably predicting pain chronification in paediatric populations. Although candidate biomarkers have been proposed across genomic, epigenomic, neuroimmune, neuroimaging, and electrophysiological domains, none currently possess sufficient validation for routine clinical implementation. The development of robust predictive biomarkers remains essential for advancing precision pain medicine in paediatric practice.[20-21]

Future research should focus on longitudinal, multimodal translational studies integrating genomic, epigenomic, proteomic, neuroimaging, and quantitative sensory phenotyping across developmental stages. Particular emphasis should be placed on identifying age-dependent windows of vulnerability, as the biological consequences of nociceptive injury likely vary according to developmental timing. Improved mechanistic phenotyping may ultimately permit individualized analgesic and preventive strategies tailored to developmental stage and underlying pain biology. (see table 2)

CONCLUSION:

Collectively, the available translational evidence supports the paradigm that paediatric pain represents a biologically distinct and developmentally dynamic entity rather than a scaled variant of adult nociception. Developmental immaturity of inhibitory pathways, heightened excitatory neurotransmission, neuroimmune priming, ion channel dysregulation, and epigenetic remodelling appear to interact in shaping age-dependent nociceptive processing and vulnerability to pain chronification. Importantly, early-life nociceptive exposure may induce persistent neuroplastic and neuroimmune alterations that extend beyond the acute injury period, providing mechanistic support for the concept of developmental nociceptive programming. These observations challenge the routine extrapolation of adult pain models to paediatric practice and highlight the limitations of empiric analgesic strategies in children. Advancing paediatric pain management will require integration of developmental neurobiology into analgesic design, alongside robust longitudinal translational studies to identify validated biomarkers, characterize critical windows of vulnerability, and enable precision-based preventive and therapeutic interventions across the paediatric age spectrum.

Declarations

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

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Author Contributions

G. Archana Gayathri contributed to study conception, literature search, data extraction, manuscript drafting, and final approval.

E. Vijayabharathi contributed to methodology development, data interpretation, critical revision of the manuscript, and final approval.

P. Krubaa contributed to data analysis, figure/table preparation, manuscript editing, and final approval.

S. Parthasarathy contributed to study supervision, conceptualization, critical review of the manuscript, and final approval of the final version.

Ethical Approval
Ethical approval was not required for this systematic review as it involved analysis of previously published studies and did not include human participants or animal experimentation directly conducted by the authors.

Informed Consent
Not applicable.

Data Availability Statement
All data generated or analyzed during this study are included in this published article.

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Table 2 PRISMA-Based Evidence Synthesis of Included Mechanistic Studies

Study (Author, Year)	Study Design	Population / Model	Sample Size	Mechanism / Biomarker Studied	Key Findings	Risk of Bias Tool	Numerical Score / Rating
Chidambaran et al., 2024	Prospective Observational Cohort	Paediatric postoperative musculoskeletal surgery patients	100+	Cytokines (IL-1β, IL-6, TNF-α)	Elevated postoperative cytokines associated with acute-to-chronic pain transition	Newcastle–Ottawa Scale	8/9
Dourson et al., 2022	Translational Review	Preclinical + Clinical Studies	Multiple Studies	Genetic/Epigenetic Regulators	Genomic and epigenomic contributors identified in postsurgical pain transition	Not Applicable	High Methodological Quality
Frangakis et al., 2023	Systematic Review & Meta-analysis	Human postsurgical pain cohorts	Multiple Studies	Genetic Variants (COMT, OPRM1, CACNG2)	Significant association between pain-related polymorphisms and postsurgical pain	Not Applicable	High Methodological Quality
Mejía-Terrazas et al., 2022	Case-Control Genetic Association	Neuropathic pain patients	290	CACNG2 Polymorphisms	CACNG2 variants associated with chronic neuropathic pain risk	Newcastle–Ottawa Scale	7/9
Bell et al., 2021	Cross-sectional Neurochemical Study	Paediatric migraine patients	29	GABA / Glutamate	Altered neurotransmitter levels linked to paediatric migraine pain states	Newcastle–Ottawa Scale	6/9
Abellán-Álvaro et al., 2026	Systematic Review	Preclinical + Clinical Studies	Multiple Studies	MeCP2 Signaling	MeCP2 implicated in pain plasticity and nociceptive modulation	Not Applicable	High Methodological Quality
Vuu et al., 2023	Experimental Molecular Study	Animal/Cellular Models	Variable	DNA Methylation / MeCP2	MeCP2 links epigenetic regulation to neuronal metabolic adaptation	SYRCLE Risk of Bias Tool	7/10
Kodila et al., 2024	Narrative Translational Review	Perinatal Trauma Models	Multiple Studies	Epigenetics / Developmental Programming	Early-life trauma alters epigenetic	Not Applicable	Moderate–High Quality

					pain regulation		
Rogan et al., 2026	Narrative Review	Paediatric Chronic Pain Literature	Multiple Studies	Neuroinflammation	Neuroimmune pathways central in paediatric chronic pain pathogenesis	Not Applicable	Moderate Quality
Guo et al., 2024	Molecular Review	Experimental Models	Multiple Studies	NF-κB Pathway	NF-κB regulates inflammatory nociceptive signaling	Not Applicable	High Quality
Pranzatelli et al., 2018	Review	Neuroinflammatory Disorders	Multiple Studies	Chemokines/Cytokines	Biomarker-guided inflammatory pathways relevant to neuroimmune pain	Not Applicable	Moderate Quality
Walker, 2008	Narrative Review	Paediatric Pain Models	Multiple Studies	Developmental Nociceptive Biology	Developmental immaturity enhances paediatric pain responses	Not Applicable	High Quality