Journal of Environmental Biology
p-ISSN: 0254-8704 • e-ISSN: 2394-0379 • CODEN: JEBIDP

JEB®

Original Research Paper
Volume 47 Issue 4 July 2026 pp. 928-934
DOI: http://doi.org/10.22438/jeb/47/4(SI)/SPL-11

J. Environ. Biol., 2026

Journal website : www.jeb.co.in ★ E-mail : editor@jeb.co.in

Bioinformatic analysis of gene networks and molecular pathways in Lesch-Nyhan Syndrome: A comprehensive enrichment study

Alfred J. Augustine[1]*, A. Sripriya[2], B. Preethi[3], S.B. Akshitha[4] and S. Vasishta[4]

[1]*Department of General Surgery, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[2]*Department of Microbiology, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[3]*Department of Dermatology, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[4]*Department of Biochemistry, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*

Received: 29 November 2025 **Revised:** 04 May 2026 **Accepted:** 30 May 2026

***Corresponding Author Email:** alfred_augustine@aimsrchittoor.edu.in ***ORCiD:** https://orcid.org/0000-0002-8393-9843

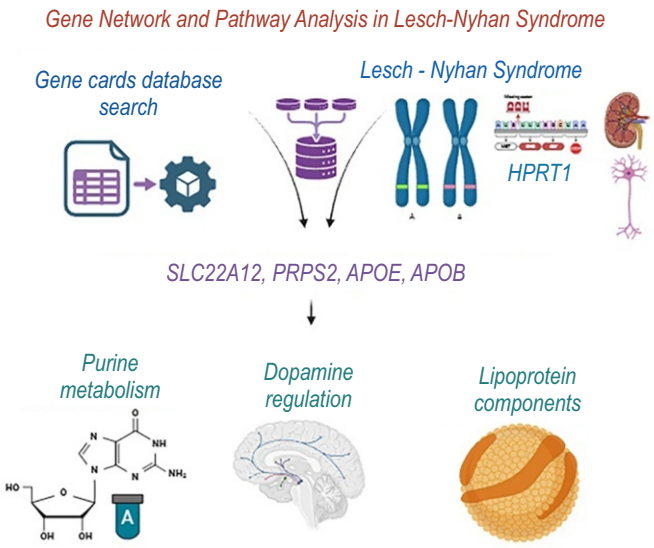
Abstract

Aim: Lesch–Nyhan syndrome (LNS) is a rare X-linked recessive disorder caused by hypoxanthine-guanine phosphoribosyl transferase deficiency, resulting in neurological dysfunction, cognitive impairment, and self-injurious behaviour. Despite longstanding clinical characterisation, molecular networks linking purine metabolism defects to systemic manifestations remain poorly understood. This study aimed to define the functional characteristics, pathway associations, transcriptional regulation, and tissue-specific expression patterns of LNS-associated genes.

Methodology: Ten LNS-implicated genes retrieved from GeneCards were analysed via Enrichr. Gene Ontology (GO) 2025 characterised biological processes, molecular functions, and cellular components. Reactome 2024 identified pathway interactions, ChEA predicted transcription factor regulation, HMDB mapped metabolite associations, and GTEx assessed tissue-specific expression. A significance threshold of $p < 0.05$ was applied.

Results: Enrichment analyses highlighted the key roles in purine metabolism, urate transport, dopamine regulation, and nucleotide biosynthesis. Implicated genes were associated with metabolic enzymes, neurotransmitter balance, and lipoprotein particle components. Transcription factor analysis identified regulatory elements governing gene expression, whilst tissue-specific patterns indicated neurological and metabolic involvement.

Interpretation: This integrative analysis connects purine metabolic dysregulation with the complex neurological and systemic features of LNS, proposing potential molecular targets warranting further preclinical investigation for therapeutic development.



Key words: Bioinformatics, Gene enrichment analysis, HPRT1 deficiency, Lesch-Nyhan syndrome, Purine metabolism

How to cite: Augustine, A. J., A. Sripriya, B. Preethi, S.B. Akshitha and S. Vasishta: Bioinformatic analysis of gene networks and molecular pathways in Lesch-Nyhan Syndrome: A comprehensive enrichment study. *J. Environ. Biol.*, **47,** 928-934 (2026).

Introduction

Lesch-Nyhan syndrome constitutes a rare yet profoundly debilitating X-linked recessive metabolic disorder first described in 1964, characterized by a triad of hyperuricemia, neurological dysfunction, and distinctive self-injurious behaviors (Tewari *et al.,* 2017). The syndrome arises from mutations in the HPRT1 gene located on chromosome Xq26-q27, encoding the enzyme hypoxanthine-guanine phosphoribosyltransferase, which catalyzes the salvage pathway conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate (Torres and Puig, 2007). Complete deficiency of this enzyme results in the classical severe phenotype, while partial deficiencies manifest as Kelley-Seegmiller syndrome with attenuated clinical features (Saigal *et al.,* 2006). The global prevalence estimates range from 1 in 100,000 to 1 in 380,000 live births, with carrier frequencies suggesting higher rates of heterozygosity in certain populations (Cauwels and Martens, 2005).

The clinical manifestations of Lesch-Nyhan syndrome emerge progressively during early childhood, with affected males initially presenting with developmental delays and hypotonia during infancy. By the second year of life, extrapyramidal motor dysfunction becomes evident, characterized by choreoathetosis, dystonia, and spasticity that severely impairs voluntary movement and coordination (Jinnah *et al.,* 2006). The pathognomonic feature of compulsive self-mutilation typically emerges between age two and three years, manifesting as aggressive biting of fingers, lips and oral mucosa, often resulting in tissue loss and requiring physical restraints or dental extraction for management (Ferrao *et al.,* 2022). Cognitive impairment varies in severity but generally falls within the mild to moderate intellectual disability range, accompanied by behavioral abnormalities including impulsivity, aggression directed toward others, and traits consistent with obsessive-compulsive disorder (Pampaloni *et al.,* 2022).

The biochemical hallmark of Lesch-Nyhan syndrome involves dramatic elevation of uric acid production, with serum concentrations frequently exceeding normal values three to four-fold. This hyperuricemia results from accelerated de novo purine synthesis compensating for the non-functional salvage pathway, leading to increased degradation of purine nucleotides to uric acid (Neychev and Mitev, 2004). Clinical consequences of hyperuricemia include nephrolithiasis with orange crystalline deposits, gouty arthritis, and potential renal failure if left untreated. The neurological manifestations, however, cannot be solely attributed to uric acid accumulation, as effective urate-lowering therapy with allopurinol prevents peripheral complications but fails to ameliorate neurological symptoms or self-injurious behaviors (Benn *et al.,* 2018). Current understanding suggests that the neurological dysfunction in Lesch-Nyhan syndrome involves profound disturbances in dopaminergic neurotransmission within the basal ganglia, particularly affecting the nigrostriatal and mesolimbic pathways. Postmortem studies and neuroimaging investigations have documented significant reductions in dopamine content and dopamine transporter density within the caudate nucleus and putamen (Ramesh and Arachchige, 2023). The precise mechanisms linking HPRT deficiency to dopaminergic dysfunction remain incompletely elucidated, though proposed hypotheses include alterations in purine-mediated neuromodulation, impaired neuronal energy metabolism, oxidative stress, and disrupted neurodevelopmental processes during critical periods of basal ganglia maturation. Despite these insights, the molecular networks connecting purine metabolism defects to the complex neuropsychiatric phenotype require comprehensive investigation using systems biology approaches.

Contemporary bioinformatic methodologies provide powerful tools for dissecting complex disease mechanisms through systematic analysis of gene networks, pathway interactions, and functional relationships. Gene enrichment analysis enables identification of overrepresented biological processes and molecular functions within gene sets, revealing coordinated patterns that may elucidate disease pathophysiology. Integration of multiple analytical platforms including Gene Ontology annotations, pathway databases, transcription factor binding data, and metabolomic associations generates comprehensive molecular portraits of disease mechanisms. Application of these approaches to Lesch-Nyhan syndrome offers opportunities to identify previously unrecognized molecular connections, potential therapeutic targets, and biomarkers for disease monitoring. This investigation employs multi-dimensional bioinformatic analysis to characterize the functional landscape of genes associated with Lesch-Nyhan syndrome, aiming to construct an integrated understanding of the molecular networks underlying this devastating disorder.

In the view of the above, we carried out to systematically characterize the functional attributes of genes associated with Lesch-Nyhan syndrome by analyzing their roles across biological processes, molecular functions, and cellular component distributions through Gene Ontology enrichment analysis. Additionally, the study aimed to explore the pathway associations, transcriptional regulatory networks, and metabolite interactions of the selected gene set using comprehensive bioinformatic databases. Furthermore, tissue-specific expression patterns and cellular localization of disease-associated genes across diverse human tissue was also assessed by leveraging data from the Genotype-Tissue Expression (GTEx) database.

Materials and Methods

The present investigation employed a systematic bioinformatic strategy to characterize genes implicated in Lesch-Nyhan syndrome pathophysiology. Gene selection was conducted using the GeneCards database (Stelzer *et al.,* 2016), from which ten key genes were curated based on relevance to the disorder and functional association with purine metabolism pathways, including *ADA, HPRT1, ADK, APOE, APP, MAOA, MAOB, AMPD1, IMPDH2,* alongside additional pathway-related

genes. Functional enrichment analysis was performed using Enrichr (Chen *et al.,* 2013), applying Gene Ontology 2025 annotations to classify genes into biological processes, molecular functions, and cellular components.

Pathway analysis employed the Reactome 2024 database (Croft *et al.,* 2014) to identify overrepresented pathways and mechanistic associations. Transcriptional regulation was explored via ChIP-X Enrichment Analysis, highlighting enriched transcription factor binding sites. Metabolite associations were identified using the Human Metabolome Database (Wishart *et al.,* 2007), linking genes with relevant substrates, products, and cofactors. Tissue-specific expression was analyzed using GTEx RNA-sequencing data, revealing distribution across tissues. Statistical rigor was ensured through significance thresholds ($p < 0.05$), multiple testing adjustments, and combined enrichment scores.

Results and Discussion

The comprehensive enrichment analysis of Lesch-Nyhan syndrome-associated genes revealed profound involvement across multiple molecular and cellular dimensions. Analysis of biological processes (Table 1) demonstrated that the gene set exhibited strongest enrichment for urate transport mechanisms, with five genes including *SLC22A12, SLC2A9, SLC22A13, SLC17A1* and *SLC17A3* participating in this process with extraordinary statistical significance (p-value 1.95×10^{-12}, combined score 2,683,821). The analysis additionally identified critical involvement in urate metabolic processes, purine-containing compound biosynthesis, and dopamine metabolism, with the latter pathway represented by *GCH1, MAOB, TH, MAOA* and *DRD1* demonstrating that neurochemical abnormalities constitute an integral component of the syndrome's molecular architecture. Further enrichment was observed for purine nucleotide biosynthetic processes, organic anion transport, regulation of protein secretion, and positive regulation of carbohydrate metabolism, collectively illustrating the multisystemic metabolic perturbations characteristic of this disorder. The dominant enrichment of urate transport genes is directly consistent with the clinical hallmark of Lesch-Nyhan syndrome, wherein defective HPRT1 activity forces hypoxanthine and guanine through degradation pathways rather than the salvage route, generating excess uric acid.

The five SLC-family transporters identified here represent the molecular machinery responsible for urate elimination, and their enrichment suggests that inter-individual variation in urate handling genes may partly determine the severity of renal complications in affected patients (Benn *et al.,* 2018). The enrichment of dopamine metabolic process genes is particularly meaningful in the context of the neurological phenotype — GCH1 encodes GTP cyclohydrolase, the rate-limiting enzyme of tetrahydrobiopterin biosynthesis, which is an obligate cofactor for tyrosine hydroxylase in dopamine synthesis. Its co-enrichment with MAOA, MAOB and DRD1 defines the complete dopaminergic regulatory axis from catecholamine biosynthesis to receptor signaling to oxidative degradation (Klein *et al.,* 2019). This is consistent with postmortem observations of severely depleted dopamine content in the basal ganglia of LNS patients and supports the view that purine deficiency indirectly impairs dopaminergic neurodevelopment during critical windows of basal ganglia maturation (Neychev and Mitev, 2004).

Cellular component analysis (Table 2) revealed distinctive subcellular localization patterns of disease-associated genes, with notable enrichment in dendritic structures where SGCE, GCHFR, APP, PRKAA2 and HTR1A localize, suggesting involvement in neuronal communication and synaptic function. Particularly striking feature was the enrichment in lipoprotein particles, with APP, APOE and APOB showing strong associations with low-density lipoprotein particles (odds ratio 110.56), triglyceride-rich plasma lipoprotein particles, and very-low-density lipoprotein particles, indicating potential connections between purine metabolism dysregulation and lipid homeostasis. Additional enrichments were identified in cell projection membranes, endocytic vesicle lumen, mitochondrial outer membrane where oxidative metabolism enzymes MAOB and

Table 1: Gene ontology biological process enrichment analysis. Statistical summary of gene associations, including p-values, adjusted p-values, odds ratios, combined scores, and corresponding genes are provided

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Urate transport (GO:0015747)	p<0.05	p<0.05	99535	2683821.01	*SLC22A12;SLC2A9;SLC22A13; SLC17A1;SLC17A3*
Urate metabolic process (GO:0046415)	p<0.05	p<0.05	274.510345	7212.0982	*SLC22A12;SLC2A9;PRPS1L1; SLC17A1;SLC17A3*
Purine-containing compound biosynthetic process (GO:0072522)	p<0.05	p<0.05	95.2325581	2393.79699	*PRPS2;ADSL;PANK2;HPRT1; PRPS1L1*
Dopamine metabolic process (GO:0042417)	p<0.05	p<0.05	105.538462	2346.06501	*GCH1;MAOB;TH;MAOA;DRD1*
Purine nucleotide biosynthetic process (GO:0006164)	p<0.05	p<0.05	75.3484848	1308.77503	*PRPS2;ADSL;HPRT1;PRPS1L1; PFAS*

Table 2: Gene ontology cellular component enrichment analysis.Columns include P-value (significance of association), Adjusted P-value (corrected for multiple testing), Odds Ratio (measure of effect size), Combined Score (integrated ranking metric), and the associated Genes

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Dendrite (GO:0030425)	p<0.05	p<0.05	8.72982706	123.242276	*SGCE;GCHFR;APP;PRKAA2;HTR1A*
Low-density lipoprotein particle (GO:0034362)	p<0.05	p<0.05	110.561111	1297.38956	*APP;APOE;APOB*
Cell projection membrane (GO:0031253)	p<0.05	p<0.05	13.5240696	154.862124	*SLC22A12;PDZK1;DRD1;DRD2; SLC17A3*
Triglyceride-rich plasma lipoprotein particle (GO:0034385)	p<0.05	p<0.05	55.2638889	556.250366	*APP;APOE;APOB*
Very-low-density lipoprotein particle (GO:0034361)	p<0.05	p<0.05	55.2638889	556.250366	*APP;APOE;APOB*

Table 3: Gene ontology molecular function enrichment analysis.p-values and adjusted p-values indicate the statistical significance, Odds Ratios represent the strength of association, and Combined Scores provide a weighted ranking of genes

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Urate transmembrane transporter activity (GO:0015143)	p<0.05	p<0.05	376.969697	8651.14024	*SLC22A12;SLC2A9;SLC22A13; SLC17A3; ABCG2*
Protein homodimerization activity (GO:0042803)	p<0.05	p<0.05	5.56448814	80.3370413	*PRPS2;APP;GCH1;TSC2;LPL*
cAMP binding (GO:0030552)	p<0.05	p<0.05	44.2044444	419.559696	*PDE10A;RAPGEF3;RAPGEF4*
Flavin adenine dinucleotide binding (GO:0050660)	p<0.05	p<0.05	16.5235123	145.11885	*MAOB;MAOA;LDHD;XDH*
Low-density lipoprotein particle receptor binding (GO:0050750)	p<0.05	p<0.05	31.5650794	271.558887	*APP;APOE;APOB*

MAOA localize, endosome lumen, neuron projections, and melanosomes, collectively demonstrating the widespread cellular distribution of disease-relevant gene products. The dendritic localization of *SGCE, GCHFR, APP, PRKAA2* and *HTR1A* is biologically relevant because dendrites are the primary sites of synaptic input integration, and disruption of dendritic protein composition can alter neurotransmitter receptor density and signal propagation. In LNS, where dopaminergic input to striatal neurons is known to be severely reduced, dendritic abnormalities in the target neurons themselves may compound the presynaptic deficit (Jinnah *et al.,* 2006).

The enrichment of APOE, APOB and APP in lipoprotein particles is an unexpected finding that warrants discussion. APOE in particular has established roles in neuronal lipid transport, synaptic membrane maintenance, and amyloid clearance. The overlap of LNS-associated genes with lipoprotein biology suggests that purine metabolic dysfunction may secondarily perturb neuronal lipid homeostasis, consistent with emerging evidence that lipid dysregulation is a feature of purine-related metabolic disorders (Yang *et al.,* 2023). The mitochondrial outer membrane localization of MAOA and MAOB is also significant, as both enzymes generate hydrogen peroxide as a by-product of amine oxidation, placing oxidative stress generation at the mitochondrial interface. Molecular function analysis (Table 3) identified urate transmembrane transporter activity as the predominant functional category, with five genes demonstrating exceptional enrichment (odds ratio 376.97, combined score 8,651). Additional significant functions included protein homodimerization activity involving fifteen genes, cyclic AMP binding with PDE10A, RAPGEF3, and RAPGEF4 participating in signal transduction pathways, and flavin adenine dinucleotide binding associated with monoamine oxidase enzymes MAOB and MAOA. The analysis further revealed enrichment for low-density lipoprotein particle receptor binding, cyclic nucleotide binding, lipoprotein particle receptor binding, oxidoreductase activity specifically acting on amine substrates, primary methylamine oxidase activity, anion binding, and zinc ion binding, collectively illustrating the diverse biochemical capabilities required for normal cellular function.

The extraordinarily high combined score for urate transmembrane transporter activity reflects the selective pressure on urate handling capacity in LNS, where chronic hyperuricemia demands efficient renal tubular secretion of uric acid. The five genes *SLC22A12, SLC2A9, SLC22A13, SLC17A3* and *ABCG2* represent distinct transporter families operating at different nephron segments, and their collective enrichment

Table 4: Reactome pathway enrichment analysis. p-value, Adjusted p-value, Odds Ratio, Combined Score, and gene names

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Metabolism of nucleotides	p<0.05	p<0.05	50.2375673	2321.13977	*ADSL;GDA;ADK;AMPD1;PFAS*
Purine salvage	p<0.05	p<0.05	269.974806	8207.70358	*DGUOK;PNP;ADK;AMPD1;HPRT1*
Metabolism	p<0.05	p<0.05	5.72716243	172.637387	*PRPS2;PRPS1;PANK2;PRKAA2;MAOB*
Nucleotide salvage	p<0.05	p<0.05	101.18968	2578.05082	*DGUOK;PNP;ADK;AMPD1;HPRT1*
Nucleotide biosynthesis	p<0.05	p<0.05	171.543103	4187.70208	*ADSL;ATIC;IMPDH2;PPAT;UMPS*

Table 5: ChIP-X enrichment analysis for transcription factor binding. Results from the gene enrichment analysis showing p-values, adjusted p-values, Odds Ratios, Combined Scores, and the corresponding genes included in the analysis

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Dopamine (HMDB00073)	p<0.05	p<0.05	124.739812	2869.88636	*MAOB;MAOA;DRD1;DRD2;SLC6A3*
Hydrogen peroxide (HMDB03125)	p<0.05	p<0.05	38.0670498	649.073157	*APP;MAOB;MAOA;CAT;XDH*
Ammonia (HMDB00051)	p<0.05	p<0.05	27.3889655	418.507513	*MAOB;GDA;MAOA;AMPD1;UPB1*
Propranolol (HMDB01849)	p<0.05	p<0.05	99.3657928	1491.33233	*ADK;HTR1A;AMPD1;APRT*
Tetrahydrobiopterin (HMDB00027)	p<0.05	p<0.05	89.4247191	1312.36096	*GCHFR;GCH1;TH;NOS1*

defines a urate secretory network that is pharmacologically targetable. Several of these transporters are already inhibited by established uricosuric agents, making them directly relevant to current therapeutic strategies (Benn *et al.,* 2018). The identification of protein homodimerization activity as a significant molecular function involving fifteen genes reflects the functional importance of protein complex formation in the LNS-associated gene network. Notably, *PRPS2* functions as a homodimer in phosphoribosyl pyrophosphate synthesis, a step directly upstream of HPRT1 in the purine salvage pathway. Disruption of dimerization-dependent enzymatic activity may, therefore, contribute to the broader metabolic imbalance seen in LNS beyond the primary HPRT1 defect. The cAMP binding enrichment involving *PDE10A, RAPGEF3* and *RAPGEF4* introduces a cyclic nucleotide signaling dimension to LNS pathophysiology. PDE10A is predominantly expressed in the striatum, where it modulates both the D1 and D2 dopamine receptor signaling cascades — two of the receptors directly identified in the biological process analysis. This places cAMP regulation at the intersection of purine catabolism and dopaminergic signal transduction (Klein *et al.,* 2019).

Pathway analysis using Reactome annotations (Table 4) demonstrated that nucleotide metabolism represented the most significantly enriched pathway category, with sixteen genes including *ADSL, GDA, ADK, AMPD1* and *PFAS* participating in this fundamental biochemical process (p-value < 0.05). Purine salvage pathways showed extraordinary enrichment with *DGUOK, PNP, ADK, AMPD1* and *HPRT1* (odds ratio 269.97, combined score 8,207), directly implicating the primary biochemical defect underlying Lesch-Nyhan syndrome. Broader metabolic pathways involving thirty-eight genes, nucleotide salvage, nucleotide biosynthesis with *ADSL, ATIC, IMPDH2, PPAT* and *UMPS,* and purine ribonucleoside monophosphate biosynthesis demonstrated coordinated involvement across multiple metabolic nodes. Additional enrichment in drug absorption, distribution, metabolism, and excretion pathways, ribavirin metabolism, pentose phosphate pathway, organic anion transport, and dopamine receptor signaling illustrated both the metabolic complexity and neurotransmitter dimensions of the syndrome.

The predominant enrichment of nucleotide metabolism and purine salvage pathways directly reflects the primary biochemical defect in LNS — the absence of functional HPRT1 means that hypoxanthine and guanine cannot re-enter the nucleotide pool via the salvage route, forcing the cell to compensate through energy-expensive de novo synthesis. This compensatory upregulation of *ADSL, ATIC, IMPDH2, PPAT* and *PFAS* represents a metabolic rebalancing that carries significant energetic costs, particularly in neurons with high ATP demands (Souckova *et al.,* 2022). The identification of dopamine receptor signaling as an enriched pathway alongside purine metabolism pathways in the same gene set is a key finding. It demonstrates that the molecular landscape of LNS extends well beyond a simple enzyme deficiency and encompasses coordinated dysfunction of neurotransmitter systems. This multi-pathway involvement explains why allopurinol, which effectively normalises uric acid levels, fails to correct neurological symptoms — the dopaminergic dysregulation has a distinct molecular basis that requires independent intervention (Balendra, 2024).

The enrichment of drug absorption, distribution, metabolism, and excretion pathways and ribavirin metabolism alongside purine salvage pathways indicates that LNS-associated genes are pharmacologically relevant beyond urate

management, with implications for personalised dosing of purine analogue drugs in affected patients. Metabolite association analysis (Table 5) revealed that dopamine represented the most significantly associated small molecule, with *MAOB, MAOA, DRD1, DRD2* and *SLC6A3* collectively participating in dopamine homeostasis (p-value 1.02×10^{-12}, combined score 2,869). This finding directly connects purine metabolism defects to the dopaminergic dysfunction underlying motor and behavioral abnormalities in affected individuals. Hydrogen peroxide associations with *APP, MAOB, MAOA, CAT* and *XDH* suggested oxidative stress involvement in pathophysiology, while ammonia associations implicated potential neurotoxic mechanisms. Additional significant metabolite associations included propranolol, tetrahydrobiopterin linking to catecholamine biosynthesis through *GCHFR, GCH1, TH* and *NOS1,* adenosine monophosphate, oxygen, inosinic acid, flavin adenine dinucleotide cofactors, D-ribose 5-phosphate, and D-ribulose 5-phosphate, collectively documenting the extensive metabolic network disruptions resulting from primary enzyme deficiency.

Dopamine as the most significantly enriched metabolite, with a combined score of 2,869, provides the strongest computational evidence for dopaminergic involvement in LNS pathophysiology generated by this analysis. The five genes contributing to this enrichment — *MAOB, MAOA, DRD1, DRD2* and *SLC6A3* — together constitute the machinery of dopamine degradation, receptor-mediated signaling, and synaptic reuptake, confirming that the LNS gene set encodes a functionally complete dopaminergic module. MAOB inhibition is already a therapeutic approach in Parkinson's disease, and the strong enrichment of MAOB in LNS metabolite associations raises the question of whether MAO inhibitors could have value in managing the neurological aspects of LNS (Ramesh and Arachchige, 2023). The hydrogen peroxide association involving APP, MAOB, MAOA, CAT and XDH is mechanistically important. Both MAO enzymes produce hydrogen peroxide during amine oxidation, and xanthine oxidase additionally generates superoxide during uric acid production. The concurrent activity of these enzymes in LNS creates a sustained oxidative environment in both peripheral tissues and the CNS. Catalase (CAT) enrichment alongside these sources indicates that the antioxidant response is engaged but may be insufficient to neutralise the chronic reactive oxygen species burden (Dash *et al.,* 2025). The tetrahydrobiopterin association through *GCHFR, GCH1, TH* and *NOS1* is clinically significant. GCH1 is the rate-limiting enzyme of BH4 synthesis, and BH4 is the cofactor not only for tyrosine hydroxylase in dopamine synthesis but also for nitric oxide synthase. BH4 deficiency would simultaneously impair dopamine production and nitric oxide-mediated vascular regulation, offering a mechanistic explanation for the multi-system features of LNS that go beyond basal ganglia dysfunction.

The bioinformatic analysis provides novel molecular insights into Lesch-Nyhan syndrome, linking purine metabolism defects to multisystemic manifestations. Enrichment of urate transporters (*SLC22A12, SLC2A9, SLC17A1*) highlights potential modifiers of uric acid–related complications. Dopamine-associated genes (*MAOA, MAOB, DRD1, DRD2, SLC6A3*) and tetrahydrobiopterin metabolism (*GCH1, GCHFR*) strongly support the dopaminergic hypothesis of neurological dysfunction (Klein *et al.,* 2019). Unexpected associations with lipid metabolism (APOE, APOB, APP) suggest overlap with neurodegenerative mechanisms (Yang *et al.,* 2023). Oxidative stress signatures, driven by xanthine oxidase and monoamine oxidase activity, together with mitochondrial and apoptotic pathway genes (*BCL2, BAX*), implicate ROS-mediated neuronal injury (Dash *et al.,* 2025). Upregulation of de novo purine synthesis (*ADSL, ATIC, IMPDH2, PPAT, PFAS*) and PRPS enzymes underscores compensatory metabolic reprogramming with energetic costs (Souckova *et al.,* 2022). Tissue-specific expression in basal ganglia, enrichment in dendritic compartments, and involvement of endocrine regulators (*IGF1, INS, PRKAA2*) emphasize synaptic, developmental, and metabolic contributions to the neurological phenotype (Lewitt and Boyd, 2019). While this study offers valuable computational insights, it is limited by the absence of experimental validation in patient samples, a focused ten-gene set, and untested clinical correlations. Nonetheless, it provides a strong foundation for future functional studies exploring dopaminergic and lipoprotein pathways underlying LNS neurological heterogeneity and treatment resistance.

Taken together, the multi-dimensional enrichment analysis reveals that Lesch-Nyhan syndrome is not simply a purine storage disorder but a complex metabolic syndrome with interconnected disruptions spanning urate handling, dopaminergic neurotransmission, lipid transport, oxidative stress, and cyclic nucleotide signaling. The convergence of these findings on the basal ganglia as the primary vulnerable region is consistent with the clinical phenotype—the striatum is simultaneously a high-dopamine region, a high-energy-demanding structure, and a site of dense MAOB expression, making it uniquely susceptible to the combined metabolic insults of HPRT1 deficiency. The unexpected identification of APOE, APOB and APP raises the possibility that lipid metabolic abnormalities may contribute to the neurodegenerative trajectory seen in some LNS patients, a dimension not previously appreciated in the classical understanding of the disease (Yang *et al.,* 2023). Future experimental studies using LNS patient-derived iPSC models or HPRT1-knockout neuronal cultures should specifically examine whether dopaminergic differentiation efficiency is reduced, whether BH4 supplementation can rescue the dopaminergic deficit, and whether lipid profiles differ from healthy controls. These studies would validate the computational predictions made here and provide mechanistic clarity needed to develop targeted neurological therapies for this presently untreatable disorder (Lewitt and Boyd, 2019).

Acknowledgment

Authors thank the Central Research Laboratory for Molecular Genetics, Bioinformatics and Machine Learning at Apollo Institute of Medical Sciences and Research Chittoor

Murukambattu-517127, Andhra Pradesh, India for the infrastructure.

Authors' contribution: Alfred J. Augustine, A. Sripriya, B. Preethi, S.B. Akshitha and S. Vasishta: All contributed equally to the study's design, data acquisition, analysis, and manuscript preparation.

Funding: Not applicable.

Research content: The research content of manuscript is original and has not been published elsewhere.

Ethical approval: Not applicable.

Conflict of interest: The authors declare that is there is no conflict of interest.

Data availability: Not applicable.

Consent to publish: All authors agree to publish the paper in *Journal of Environmental Biology.*

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