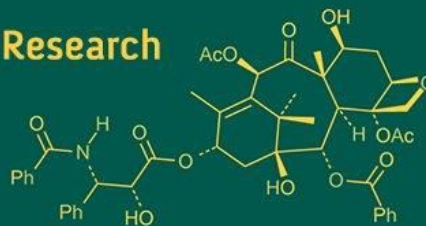
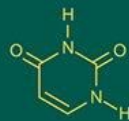
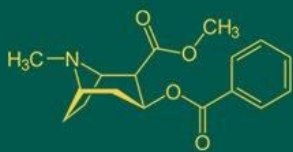


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating (2026): 5.29
IJABR 2026; 10(4): 247-252
www.biochemjournal.com
Received: 21-02-2026
Accepted: 23-03-2026

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Integrative transcriptomic analysis reveals GCH1 and Coasy as key regulators in cypermethrin-induced lung dysfunction

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DOI: <https://www.doi.org/10.33545/26174693.2026.v10.i4d.8097>

Abstract

Cypermethrin, a commonly used pyrethroid insecticide, is known to induce respiratory toxicity through complex metabolic and oxidative disturbances. In this study, transcriptomic and bioinformatic analyses were performed to uncover the molecular mechanisms underlying cypermethrin-induced pulmonary dysfunction. Gene Ontology and protein-protein interaction network analyses revealed significant alterations in mitochondrial energy metabolism and redox regulation. Among the identified targets, *Gch1* and *Coasy* emerged as key molecular hubs. *Gch1* governs tetrahydrobiopterin biosynthesis, influencing nitric oxide signaling and antioxidant defense, while *Coasy* regulates the final step of coenzyme A biosynthesis, crucial for fatty acid oxidation and tricarboxylic acid cycle activity. The concurrent dysregulation of these genes indicates disrupted cofactor balance, mitochondrial impairment, and oxidative stress, ultimately compromising cellular homeostasis and lung function. These findings highlight *Gch1* and *Coasy* as potential biomarkers and therapeutic targets for assessing and mitigating cypermethrin-induced pulmonary toxicity.

Keywords: Cypermethrin, respiratory toxicity, transcriptomics, gch1, Coasy

Introduction

Pesticides are extensively employed to control a wide range of insect pests, weeds, and other harmful organisms in agricultural ecosystems. Beyond agricultural applications, they are also utilized in non-agricultural settings such as hospitals, schools, lawns, and industrial areas to manage vector-borne diseases (Mahmood *et al.*, 2016). Agriculture, a principal pillar of the Indian economy (Madhusudhan, 2015), is currently challenged by escalating food insecurity as emerging pest species broaden their host range and exhibit increasing resistance to conventional pesticides (Rathee & Dalal, 2018) [24, 35].

Globally, pesticide consumption is estimated at approximately 4 million tonnes per annum, comprising 47% herbicides, 29% insecticides, 17% fungicides, and 5% other categories (Sharma *et al.*, 2019). Within India, Maharashtra records the highest pesticide usage (13,243 M.T. Technical Grade), followed by Uttar Pradesh (11,557 M.T.) and Punjab (5,193 M.T.) (GOI, 2021) [14, 43].

Cypermethrin, a synthetic type II pyrethroid insecticide, was first introduced in 1977 under Section 9(3) of the Insecticides Act, 1968. It is structurally derived from naturally occurring pyrethrins, conferring enhanced photostability and environmental persistence compared to its natural analogues. Cypermethrin is widely used to mitigate yield losses by effectively targeting key insect pests such as bollworms, shoot and fruit borers of okra, and jassids. However, its extensive application and high environmental persistence have raised ecological concerns due to its toxic effects on non-target, economically significant organisms including pollinators (bees), soil fauna (earthworms), and aquatic species (fish) (Kumar *et al.*, 2009; Nie *et al.*, 2020) [19, 31].

Pesticide residues present in drinking water, fruits, and vegetables constitute one of the primary routes of exposure for the general population (Damalas & Eleftherohorinos, 2011). Cypermethrin exhibits pronounced toxicity in aquatic ecosystems due to its solubility and persistence in water bodies (Helfrich *et al.*, 2009), while in terrestrial organisms, it exerts deleterious effects through bioaccumulation in tissues (Mahmood *et al.*, 2016) [6, 16, 24].

In humans, excessive accumulation of cypermethrin can result in both acute and chronic toxic manifestations. Acute exposure is commonly associated with symptoms such as headache, dizziness, vomiting, abdominal discomfort, and dermal irritation, whereas chronic exposure has been implicated in functional impairments of the lungs, liver, kidneys, brain, and reproductive system, with emerging evidence suggesting its potential carcinogenicity (Sabarwal *et al.*, 2018) [37].

Experimental findings from our laboratory have demonstrated that prolonged oral administration of chlorpyrifos and/or cypermethrin in murine models induces marked pulmonary toxicity characterized by inflammatory and degenerative changes (Chougule *et al.*, 2013; Nazki *et al.*, 2019; Sethi *et al.*, 2017; Shaikh & Sethi, 2020; Shaikh & Sethi, 2021) [5].

Several studies have described the toxicological effects of cypermethrin on pulmonary tissues in experimental animal models (Chougule *et al.* 2013; Sethi *et al.* 2017; Nazki *et al.* 2019; Shaikh and Sethi 2020; Shaikh and Sethi 2021; Nair *et al.* 2010). Cypermethrin exposure has been shown to induce marked pulmonary damage, with histopathological alterations such as alveolar collapse, oedema, haemorrhage, vascular congestion, and fibroplasia reported in rats and mice (Grewal *et al.* 2009; Nair *et al.* 2010) [5, 15, 28, 30].

Additionally, studies have demonstrated pesticide-induced dysregulation of several molecular pathways, including the PCP pathway (Pandit *et al.* 2019), small cell lung cancer pathway (Kaur *et al.* 2021), and apoptosis pathway (Shaikh and Sethi 2021) in the lungs of exposed mice. Furthermore, disruption of metabolic regulation may lead to insulin resistance, predisposing individuals to metabolic disorders (Yaribeygi *et al.* 2019) [17, 32, 40, 41, 42].

At present, the current bioinformatic pilot study is being carried out to find out any potential marker from the published literature on which studies has not been carried out and require further studies. In other words, this article adds on to the previous literature and short list the pulmonary genes for a complete study focusing on marker-based lung health monitoring.

Data Collection

In the present study, the identification of key genes associated pulmonary dysregulation following cypermethrin exposure was carried out through bioinformatic exploration of publicly available transcriptomic datasets and extensive literature-based evidence. The analysis focused on genes reported to play significant roles in mitochondrial function, oxidative stress regulation, and pulmonary tissue homeostasis (Tiwari *et al.*, 2012; Rodrigues *et al.*, 2022). Special attention was given to molecular markers involved in core metabolic pathways, energy production, redox balance, and coenzyme biosynthesis, as well as genes implicated in lung development, function, and disease progression (Sugden & Holness, 2011; Ferdinandusse *et al.*, 2013; Selen *et al.*, 2022; Kong *et al.*, 2023; Podczek *et al.*, 2020) [10, 18, 34, 36, 38, 45, 46].

The gene pool considered for analysis included a wide range of metabolic and lung-function-associated candidates such as *TMEM163*, *CDC123*, *HHIP*, *FAM13A*, *AGER*, *SERPINE1*, *SOCS3*, *CRABP2*, *SLC38A8*, *MMP12*, *IL6*, *FAM83A*, *FAM83B*, *FOXP4*, *DPP9*, *NPNT*, *MECOM*, *LTBP4*, *EFEMP1*, *TERT*, *TERC*, *RTEL1*, *PARN*, *ORMDL3*, *AQP1*, *IL6R*, *TNS1*, *SCNN1B* and *Pcx*, *CYTB*, *Gch1*, *HIBCH*, and *Coasy*. These genes have been widely reported in genome-

wide association studies and molecular expression analyses to contribute to oxidative balance, immune modulation, extracellular matrix organization, telomere maintenance, and overall lung tissue integrity (Shrine *et al.*, 2023; Garcia *et al.*, 2022; Fricke-Galindo *et al.*, 2025; MDPI, 2024; BioMed Central, 2023) [2, 11, 12, 26, 44].

Materials and Methods

Data Collection: The identification of key genes associated with pulmonary dysregulation following cypermethrin exposure was carried out through a comprehensive bioinformatic exploration of publicly available transcriptomic datasets and literature-based evidence. The analysis primarily focused on genes known to regulate mitochondrial function, oxidative stress response, and pulmonary tissue homeostasis (Tiwari *et al.*, 2012; Rodrigues *et al.*, 2022) [36, 46].

Special emphasis was placed on molecular markers involved in energy metabolism, redox balance, coenzyme biosynthesis, and lung tissue integrity, as well as those implicated in inflammation, immune modulation, and extracellular matrix remodeling (Sugden and Holness, 2011; Ferdinandusse *et al.*, 2013; Selen *et al.*, 2022; Kong *et al.*, 2023; Podczek *et al.*, 2020) [10, 18, 34, 38, 45].

The curated gene panel included *TMEM163*, *CDC123*, *HHIP*, *FAM13A*, *AGER*, *SERPINE1*, *SOCS3*, *CRABP2*, *SLC38A8*, *MMP12*, *IL6*, *FAM83A*, *FAM83B*, *FOXP4*, *DPP9*, *NPNT*, *MECOM*, *LTBP4*, *EFEMP1*, *TERT*, *TERC*, *RTEL1*, *PARN*, *ORMDL3*, *AQP1*, *IL6R*, *TNS1*, *SCNN1B*, *PCX*, *CYTB*, *GCH1*, *HIBCH*, and *COASY* all previously associated with mitochondrial activity, oxidative regulation, and lung disease susceptibility (Miller *et al.*, 2016; Castaldi *et al.*, 2019; Shrine *et al.*, 2023; Garcia *et al.*, 2022; Cavestro *et al.*, 2024; Werder, 2024; Fricke-Galindo *et al.*, 2025) [3].

Recent transcriptomic insights were also incorporated from genomic databases and recent reviews (MDPI, 2024; BioMed Central, 2023; GeneCards, n.d.), allowing for the inclusion of emerging molecular targets linked to pesticide-induced pulmonary toxicity [2, 4, 12, 13, 26, 47].

This integrative approach provided a holistic understanding of how chronic cypermethrin exposure may disrupt key regulatory and metabolic pathways associated with oxidative stress, mitochondrial dysfunction, and inflammatory signaling. Such integration facilitated the identification of candidate biomarkers for cypermethrin-induced lung alterations (Shrine *et al.*, 2023; Fricke-Galindo *et al.*, 2025; Miller *et al.*, 2016) [11, 27, 44].

Pathway Analysis: Functional enrichment of the gene dataset was conducted using the Database for Annotation, Visualization and Integrated Discovery (DAVID), with *Mus musculus* selected as the reference organism. Gene identifiers were submitted using the *Official_Gene_Symbol* format.

The analysis highlighted major pathways through Kyoto Encyclopedia of Genes and Genomes (KEGG) annotation. Among these, metabolic pathways, oxidative phosphorylation, and biosynthesis of cofactors were most enriched consistent with previous findings on mitochondrial toxicity caused by pyrethroid exposure (Bharathi *et al.*, 2020; Nandi *et al.*, 2005; Li *et al.*, 2020) [1, 29].

Gene Ontology (GO) Analysis

Gene Ontology (GO) classification was carried out using the PANTHER database, organizing genes into categories of

biological process, molecular function, cellular component, and protein class. The analysis revealed strong associations with catalytic activity, oxidoreductase activity, ATP-binding, and transporter functions, signifying mitochondrial energy disruption and oxidative imbalance (Kong *et al.*, 2023; Selen *et al.*, 2022) [18, 38].

Protein-Protein Interaction (PPI) Analysis

To elucidate functional interconnectivity among the identified proteins, STRING v12.0 was used to construct a protein-protein interaction (PPI) network based on co-expression, co-occurrence, and experimental validation parameters. The PPI results indicated a strong mitochondrial-centered module with key metabolic enzymes forming a dense interaction network.

Within this cluster, GCH1 (GTP cyclohydrolase 1) and COASY (Coenzyme A synthase) emerged as central regulatory nodes, highlighting their pivotal role in tetrahydrobiopterin biosynthesis, cofactor metabolism, and energy homeostasis. This supports their selection as candidate markers of cypermethrin-induced mitochondrial stress and pulmonary dysfunction (Peters *et al.*, 2015; Dusi *et al.*, 2014; Li *et al.*, 2020) [9, 33].

Results

The bioinformatic evaluation of cypermethrin-associated transcriptomic datasets revealed a distinct pattern of gene expression changes indicative of metabolic and regulatory dysfunction in the lungs. Gene Ontology (GO) enrichment analysis performed through the PANTHER database categorized the differentially expressed genes primarily under biological processes related to metabolism, cellular response to stress, immune regulation, and homeostasis, suggesting that cypermethrin exposure disrupts both energy metabolism and defense mechanisms within pulmonary tissues.

In the molecular function category, significant enrichment was observed for catalytic activity, binding, transporter activity, transcription regulation, and ATP-dependent processes, reflecting broad perturbations in enzyme function, molecular signaling, and energy transfer mechanisms. These alterations collectively point toward mitochondrial and metabolic stress, leading to impaired cellular homeostasis and reduced respiratory efficiency in lung tissue (Miller *et al.*, 2016; Castaldi *et al.*, 2019; Werder, 2024; Cavestro *et al.*, 2024; Shrine *et al.*, 2023; Garcia *et al.*, 2022; Fricke-Galindo *et al.*, 2025) (Figure 1) [3, 4, 11, 12, 27, 44, 47].

Pathway analysis through the DAVID and KEGG platforms further highlighted oxidative phosphorylation, metabolic pathways, and biosynthesis of cofactors as the most affected functional categories. This pattern indicates that cypermethrin-induced toxicity is not solely a consequence of oxidative stress, but also involves disruption of fundamental biochemical pathways essential for cellular energy production and antioxidant defense (Peixoto and Rocha, 2021).

The integration of diverse gene datasets encompassing candidates such as *TMEM163*, *CDC123*, *HHIP*, *FAM13A*, *AGER*, *SERPINE1*, *SOCS3*, *CRABP2*, *SLC38A8*, *MMP12*, *IL6*, *FAM83A*, *FAM83B*, *FOXP4*, *DPP9*, *NPNT*, *MECOM*, *LTBP4*, *EFEMP1*, *TERT*, *TERC*, *RTEL1*, *PARN*, *ORMDL3*, *AQP1*, *IL6R*, *TNSI*, *SCNN1B*, *PCX*, *CYTB*, *GCH1*, *HIBCH*, and *COASY* enabled a holistic understanding of molecular

perturbations associated with cypermethrin toxicity. These genes have been widely reported in genome-wide association and expression studies to influence oxidative balance, immune modulation, extracellular matrix organization, telomere maintenance, and lung tissue integrity (Shrine *et al.*, 2023; Garcia *et al.*, 2022; Fricke-Galindo *et al.*, 2025; MDPI, 2024; BioMed Central, 2023) [2, 11, 12, 26, 44].

Protein-protein interaction (PPI) network analysis using STRING revealed a highly interconnected module of mitochondrial and metabolic enzymes, representing a coordinated response to cypermethrin-induced metabolic stress (Figure 2). Within this cluster, two genes *GTP cyclohydrolase 1 (Gch1)* and *Coenzyme A synthase (Coasy)* were identified as key regulators of cofactor and energy metabolism.

Discussion

Central Role of Gch1 and Coasy

Protein-protein interaction analysis identified *Gch1* and *Coasy* as central regulatory nodes linking oxidative stress response, energy metabolism, and cofactor biosynthesis. Their network proximity suggests a coordinated function in maintaining mitochondrial integrity and cellular redox balance under cypermethrin-induced stress.

Gch1: Regulator of Nitric Oxide Homeostasis and Redox Equilibrium

Gch1 catalyzes the rate-limiting step in tetrahydrobiopterin (BH4) biosynthesis, a critical cofactor for nitric oxide synthase (NOS) activity and antioxidant defense. Under normal physiological conditions, adequate BH4 ensures proper NOS coupling, allowing nitric oxide (NO) production that supports vascular tone, mitochondrial respiration, and oxidative equilibrium. Suppression of *Gch1* expression, as indicated in this analysis, may lead to BH4 depletion and NOS uncoupling, resulting in superoxide rather than NO formation. This imbalance promotes reactive oxygen species (ROS) accumulation, nitrosative stress, and pulmonary endothelial dysfunction, thereby enhancing inflammatory signaling (Peixoto and Rocha, 2021). Reduced *Gch1* activity may further impair NO-mediated signaling and activate redox-sensitive transcription factors such as *Nfe2l2* and *Tnf*, both of which drive oxidative injury and fibrotic remodeling in lung tissue (Zhao *et al.*, 2022) [48].

Coasy: Metabolic Regulator of Mitochondrial Energy Dynamics

In parallel, *Coasy* catalyzes the final step in coenzyme A (CoA) biosynthesis, converting dephospho-CoA to its active form an essential cofactor for fatty acid oxidation, amino acid catabolism, and tricarboxylic acid (TCA) cycle activity (Dusi *et al.*, 2014). CoA serves as a key metabolic integrator, channeling acetyl groups into oxidative phosphorylation for ATP generation. Downregulation of *Coasy* impairs this pathway, leading to energy depletion, accumulation of metabolic intermediates, and diminished mitochondrial efficiency (Ogasawara *et al.*, 2020). These effects collectively promote mitochondrial stress, excessive ROS production, and compensatory metabolic shifts, contributing to chronic oxidative injury and inflammation [9].

Functional Co-expression and Integrated Mechanism

The co-expression of *Gch1* and *Coasy* underscores their

interdependence in maintaining metabolic-redox homeostasis. *Gchl* sustains antioxidant defenses through BH4-dependent NOS regulation, while *Coasy* ensures continuous CoA supply for oxidative metabolism. Their simultaneous downregulation under cypermethrin exposure suggests a dual-hit mechanism in which disruption of both cofactor biosynthesis and energy metabolism amplifies mitochondrial dysfunction and oxidative stress (Li *et al.*, 2020; Singh *et al.*, 2023). This cascade destabilizes electron transport, activates inflammatory mediators, and promotes epithelial-mesenchymal transition (EMT), ultimately predisposing to fibrotic remodeling and chronic pulmonary injury.

Toxicological Implications

Collectively, *Gchl* and *Coasy* act as molecular sentinels integrating redox regulation and mitochondrial metabolism. Their centrality within the metabolic-redox interaction network delineates a mitochondria-centered mechanism of cypermethrin-induced pulmonary toxicity. The dysregulation of these genes highlights a biochemical axis linking oxidative

imbalance, bioenergetic insufficiency, and inflammatory progression positioning *Gchl* and *Coasy* as potential biomarkers and therapeutic targets for pesticide-related lung disorders.

Conclusion

The integrative transcriptomic and PPI analyses underscore *Gchl* and *Coasy* as pivotal molecular determinants bridging oxidative stress, mitochondrial dysfunction, and inflammatory activation in cypermethrin-induced lung injury. Functional impairment of *Gchl* compromises tetrahydrobiopterin-dependent nitric oxide and antioxidant pathways, whereas downregulation of *Coasy* disrupts coenzyme A biosynthesis and mitochondrial ATP generation. These synergistic perturbations initiate a feedback loop of oxidative stress, energy failure, and inflammation, consistent with early hallmarks of chronic pulmonary pathology. Overall, this mitochondria-centric framework identifies *Gchl* and *Coasy* as promising targets for the early detection and mitigation of pesticide-induced pulmonary toxicity.

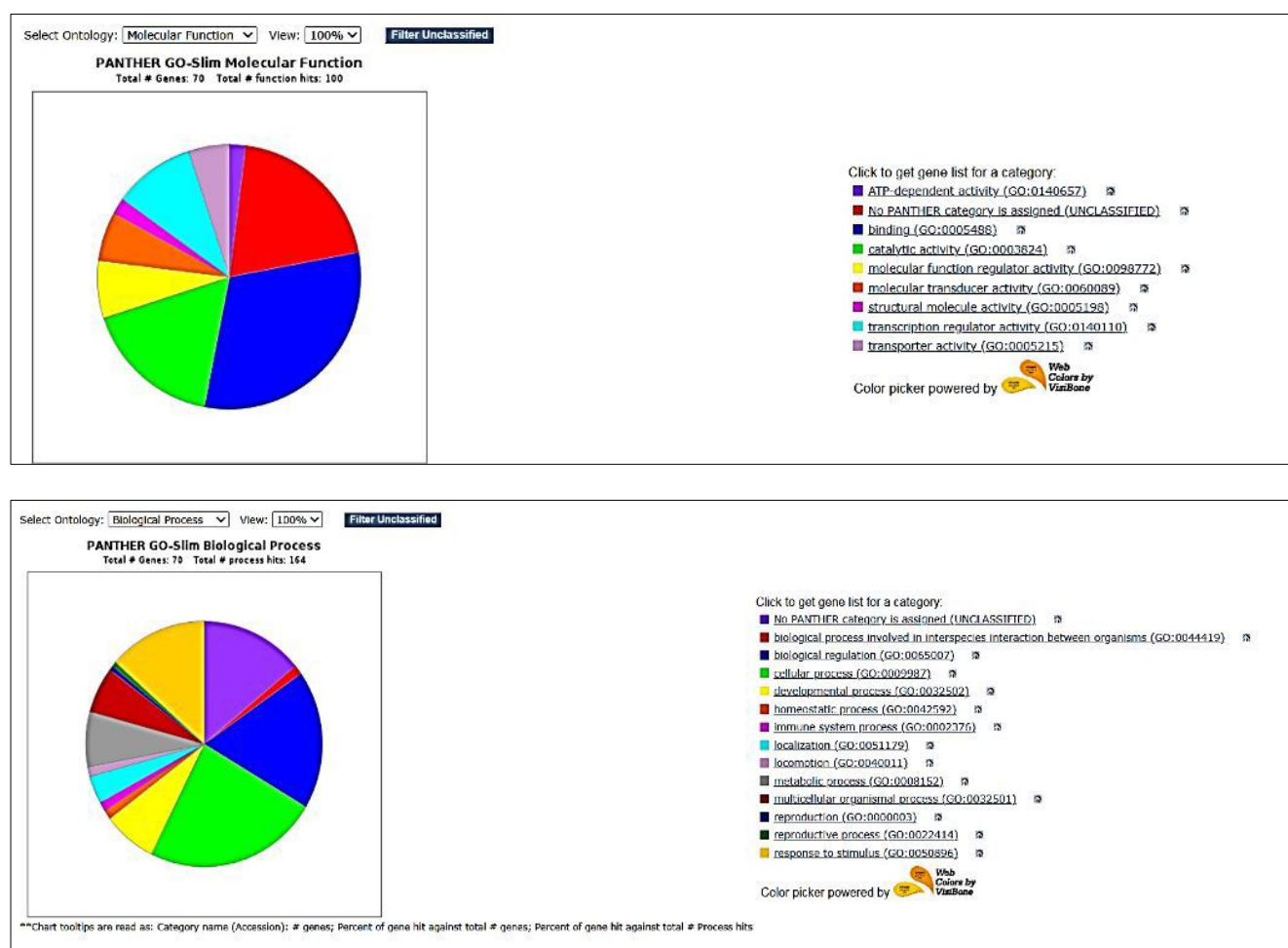


Fig 1: Molecular and Biological significance of genes following exposure to Cypermethrin.

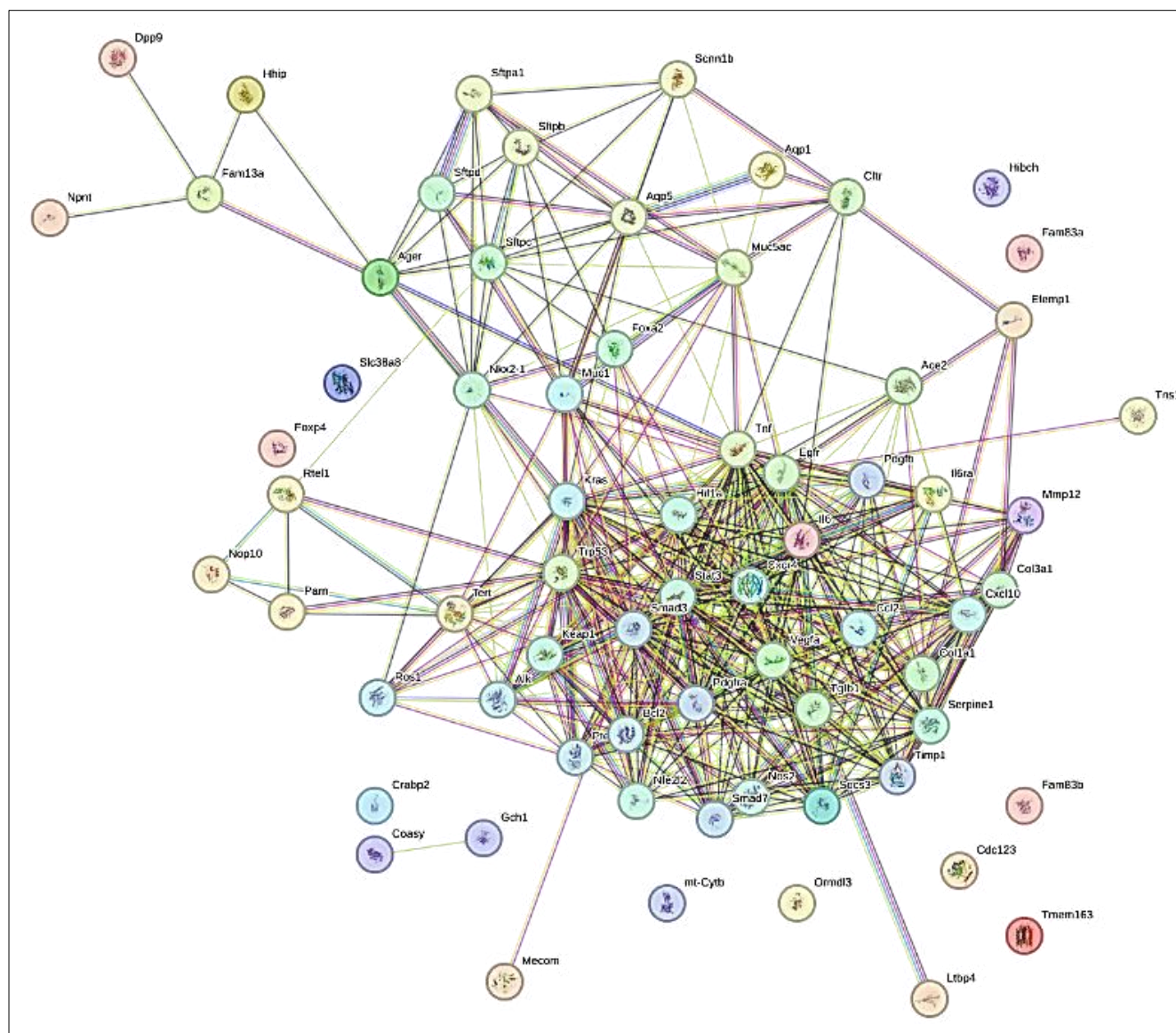


Fig 2: PPI network of gene data collected from published data following exposure to Cypermethrin

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