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Functional gene analysis in Tay-Sachs disease using enrichment tools

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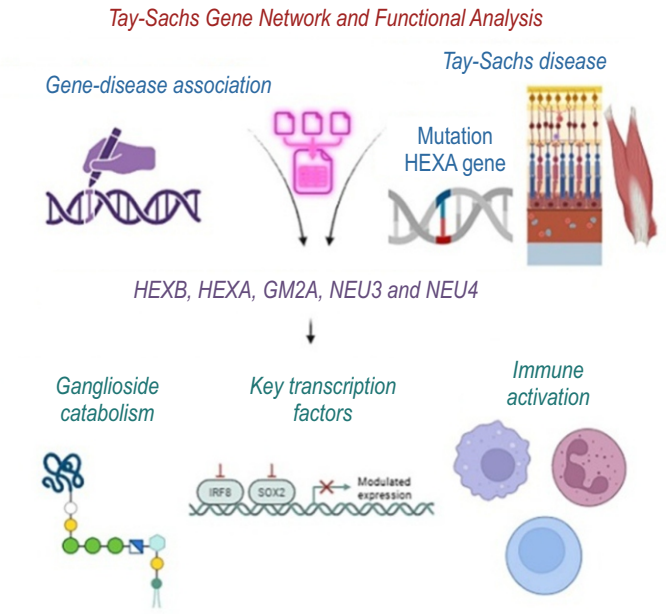
Abstract

Aim: Tay-Sachs disease is a rare autosomal recessive neuro-degenerative disorder arising from β-Hexosaminidase A deficiency, predominantly affecting consanguineous families. Given limited molecular-level characterisation, this study aimed to functionally annotate disease-associated genes, delineate fundamental pathways, regulatory elements, and metabolite and co-disease interactions.

Methodology: Tay-Sachs-associated genes were retrieved from DisGeNET (CUI: C0039373) via Enrichr. Gene Ontology (2025) facilitated annotation across molecular function, biological process, and cellular component categories. Pathway associations were identified using Reactome (2024), transcription factor linkages via ChEA, metabolite associations through HMDB, and co-disease mapping via DisGeNET. A significance threshold of $p < 0.05$ was applied throughout.

Results: Key genes including *GLB1, HEXB, HEXA, GM2A, NEU3* and NEU4 were enriched for ganglioside and glycosphingolipid catabolism, hexosaminidase activity and glycoside hydrolase activity, predominantly localising to lysosomal and vacuolar compartments. Transcription factors *SOX2, IRF8* and *NANOG* were linked to pluripotency and immune pathways. Metabolite profiling implicated gangliosides, reinforcing dysregulation within sphingolipid metabolic pathways.

Interpretation: This integrative bioinformatic analysis consolidates the molecular and metabolic architecture of Tay-Sachs disease, identifying key genetic and regulatory contributors that may serve as a foundation for future experimental validation.



Key words: GM2 gangliosidosis, Hexosaminidase-A deficiency, Lysosomal storage disorder, Sphingolipidosis

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Introduction

Tay-Sachs disease is one of the most crippling lysosomal storage ailments, boasting an inexorable progression of neurological deterioration that usually begins in young children and ends in precariously early deaths (Lui *et al.,* 2026). This autosomal recessive disorder follows mutations within the HEXA gene, coding the alpha subunit of the lysosomal enzyme Hexosaminidase A, causing an untimely accumulation of GM2 gangliosides in neuronal lysosomes (Lopshire *et al.,* 2023). The traditional infantile form usually begins in infancy, around three to six months of age, with symptoms of regression, cherry-red spots in the macula, hyperacusis, and progressive motor impairment, culminating in death in children aged five (Maegawa *et al.,* 2006). This disease portrays an unprecedented degree of genetic diversity, boasting an impressive 130+ mutations within the HEXA gene, each imparting varying levels of enzymatic activity in tandem with phenotypes (Ibrahim *et al.,* 2023).

There have been remarkable founder effects identified among certain communities, especially among Ashkenazi Jews, where the carrier frequency has been estimated to be one in twenty-seven, which translates to nearly a hundred times the incidence as that among the general population. There are also parallel patterns of enrichment seen among the French-Canadian population of the province of Quebec, as well as those of the Louisiana Cajun population, as well as among the Pennsylvania Dutch population, due to past founder effects or consanguineous marriages. Interestingly, recent studies have also identified that consanguineous marriage carries with it a remarkable level of impact that translates to the incidence of the disease, as the families have been identified to have a carrier status of nearly 33% (Khayat *et al.,* 2024). The biochemical basis for pathogenesis is related to impaired hydrolytic cleavage of N-acetyl galactosamine from GM2 gangliosides, a process requiring the combined action of three different gene products: the alpha and beta subunits of hexosaminidase itself, produced from hexosaminidase genes HEXA and HEXB, and the GM2 activator protein produced from the GM2A gene.

This enzymatic enzyme functions in the low pH lysosomal environment necessary for the multi-step degradation process necessary for ganglioside degradation--crucial remnants found in large numbers in the gray matter cellular environment primarily composing the neuronal membrane (Deschenes *et al.,* 2023). As hexosaminidase-A enzymatic activity decreases to a critical level lower than 10% activity in lysosomes, there is a disastrous series of cellular abnormalities due to GM2 ganglioside accumulation followed by apoptosis/necrosis (Leal *et al.,* 2020). Symptoms differ to a great degree according to the subtype of the disease, ranging from that described as classic infantile with onset before six months of life with acute progression, to juvenile with onset between two to five years with a slower progression, to final ones with onset in adulthood with psychiatric disturbance, motor neuron disease, and cerebellar ataxia with preservation of intelligence (King *et al.,* 2020).

At present, the available treatments are mainly supportive in nature and consist of the following: administration of antiepileptic drugs for seizure control, nutritional support using a gastrostomy tube, pulmonary hygiene for the purpose of aspiration prevention, and extensive palliative management. Experimental therapies available are: the use of substrate reduction therapy with migalastat in the reduction of ganglioside biosynthesis, the use of enzyme replacement therapy and the hurdles of crossed blood-brain barriers, the use of gene therapy with the administration of viral vectors for the introduction of the HEXA gene, and the use of pharmacological chaperones in attempts to stabilize mutant enzymes (Toro *et al.,* 2021). Also available, though with proven efficacy only in presymptomatic patients with the juvenile forms, are hematopoietic stem cell transplantations with varying benefits in the nervous systems (de Vasconcelos and Lacerda, 2022).

The molecular pathogenesis of Tay-Sachs disease has been incompletely understood despite extensive clinical characterization. Classic gene-centric studies lack an integrative insight into unraveling the complex molecular networks underlying Tay-Sachs disease. Advances in computational biology now enable the identification of key genes, pathways, and therapeutic targets through systems-level bioinformatics analyses with comprehensive enrichment approaches. Therefore, this study aims to investigate the molecular architecture of Tay-Sachs disease through multi-dimensional enrichment analysis of disease-associated genes retrieved from DisGeNET, using Gene Ontology, Reactome pathway analysis, ChIP-X transcription factor enrichment, and Human Metabolome Database annotations (Asim *et al.,* 2025), in order to functionally characterise associated molecular processes, identify key therapeutic targets, and elucidate shared pathogenic pathways with related lysosomal storage disorders.

Materials and Methods

The genes associated with diseases for Tay-Sachs disease were extracted from DisGeNET (Piñero *et al.,* 2020) with CUI: C0039373. Gene function was analyzed based on Gene Ontology (Roncaglia *et al.,* 2013) classifications in the year, 2025. Genes are categorized based on their molecular function, biological processes, and cellular components to describe functions at a biochemical level, as well as processes and components at the cellular and organism level.

Pathway Enrichment Analysis: Pathway enrichment analysis was done using Reactome (Vastrik *et al.,* 2007) version, 2024, the manually curated knowledge base, to explore pathway over-representation in Tay-Sachs disease. Transcriptional regulatory networks were investigated using ChIP-X Enrichment Analysis (ChEA), which uses ChIP-Seq or ChIP-chip data to identify transcription factors that are preferentially associated with genes that are implicated in diseases to uncover upstream programs that regulate coordinated expression. Associations for the metabolites were assessed through use of the Human

Table 1: Gene ontology biological process enrichment analysis for tay-sachs disease-associated genes

Terms	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Ganglioside catabolic process (GO:0006689)	p<0.05	2.67E-14	4992.25	187720.89	*NEU3;NEU4;GM2A;GLB1;HEXB*
Glycosphingolipid catabolic process (GO:0046479)	p<0.05	2.67E-14	675.009662	24932.5934	*NEU3;NEU4;GM2A;GLB1;HEXB*
Ceramide catabolic process (GO:0046514)	p<0.05	1.04E-11	499	15254.0373	*NEU3;NEU4;GM2A;GLB1;HEXB*
Ganglioside metabolic process (GO:0001573)	p<0.05	3.75E-11	356.357143	10333.0527	*NEU3;NEU4;GM2A;GLB1;HEXB*
Glycolipid catabolic process (GO:0019377)	p<0.05	4.79E-07	307.076923	5932.40267	*NEU3;GM2A;GLB1;SMPD1*

Table 2: Gene ontology cellular component enrichment analysis for Tay-Sachs disease associated genes

Terms	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Lysosomal lumen (GO:0043202)	p<0.05	3.04E-13	110.721707	3661.65153	*ARSA;CSF3;NEU4;GM2A;IDUA*
Vacuolar lumen (GO:0005775)	p<0.05	5.49E-11	55.1465677	1498.92708	*ARSA;CSF3;NEU4;GM2A;IDUA*
Lysosome (GO:0005764)	p<0.05	1.45E-10	24.9358974	643.48791	*NEU3;ARSA;CSF3;NEU4;GM2A*
Lytic vacuole (GO:0000323)	p<0.05	2.73E-08	31.4864434	638.46554	*NEU3;ARSA;NEU4;GLB1;HEXB*
Azurophil granule (GO:0042582)	p<0.05	0.0000447	26.4266667	334.414087	*ARSA;GM2A;GLB1;HEXB;HEXA*

Metabolome Database (HMDB) (Wishart *et al.,* 2018), where small molecules known to be involved in the biosynthesis, degradation, or transport processes affected by genes responsible for Tay-Sachs disease were found. Co-disease mapping was conducted through the use of disease similarity algorithms in the DisGeNET database. The level of statistical significance was evaluated using $p < 0.05$, with correction for multiple hypothesis testing by Benjamini-Hochberg false discovery rate. The extent of enrichment or biological significance was further refined by odds ratios. All analyses were done by using web-based bioinformatics tools to avoid inconsistencies.

Results and Discussion

The enrichment analysis of genes associated with Tay-Sachs disease helped identify major molecular mechanisms in lysosomal dysfunction. The biological process enrichment analysis is presented in Table 1. The ganglioside catabolic process (GO:0006689) had major enrichment significance ($p < 0.05$, combined score of 187,720.89), suggesting NEU3, NEU4, GM2A, GLB1, and HEXB involvement. The glycosphingolipid catabolic process (GO:0046479) also had equal significance ($p < 0.05$, odds ratio of 675.01), whereas ceramide catabolic process (GO:0046514) and ganglioside metabolic process (GO:0001573) also portrayed significant enrichment, suggesting derangements in lipid metabolism. Moreover, glycolipid and glycoprotein catabolic processes, sphingolipid catabolism, and glycosaminoglycan metabolism, collectively revealed the coordinated nature of lysosomal degradative pathways. The strong enrichment of ganglioside catabolic process with a combined score exceeding 187,000 is a direct reflection of primary biochemical defect in Tay-Sachs disease, where deficiency of Hexosaminidase A leads to progressive accumulation of GM2 gangliosides within neuronal lysosomes (Deschenes *et al.,* 2023). The involvement of NEU3 and NEU4 alongside the classical TSD genes GM2A, GLB1 and HEXB in these enriched terms suggests that sialidase activity also participates in the broader ganglioside degradation network, and disruption of this coordinated process amplifies the substrate burden in affected neurons (Allende *et al.,* 2023). The concurrent enrichment of ceramide and glycolipid catabolic processes further indicates that the metabolic blockade in TSD is not limited to GM2 alone but extends across the sphingolipid degradation cascade, pointing to a more systemic lysosomal dysfunction than previously appreciated (Leal *et al.,* 2020). It is also worth noting that glycoprotein catabolic processes and glycosaminoglycan metabolism appeared among the enriched terms, which suggests that the metabolic derangement in TSD has broader consequences for extracellular matrix maintenance and cell surface glycan processing in the central nervous system. These findings are consistent with the reports of secondary storage of other glycoconjugates in GM2 gangliosidosis models, where the primary enzymatic block leads to downstream accumulation of related substrates (Toro *et al.,* 2021).

Cell component analysis (Table 2) confirmed lysosomal lumen (GO:0043202) and vacuolar lumen (GO:0005775) as major targeted locations for gene expression, scoring 3,661.65 and 1,498.93, respectively. Lysosome (GO:0005764),_lytic vacuole (GO:0000323), primary lysosome (GO:0005766), azurophil granule (GO:0042582), and secretory granule lumen also showed significant enrichment, implicating both classical lysosomal function and immune-related pathways. The predominant localisation of disease-associated genes to the lysosomal lumen and vacuolar lumen is consistent with the fundamental pathology of Tay-Sachs disease, where substrate

Table 3: Gene ontology\molecular function enrichment analysis for Tay-Sachs disease-associated genes

Terms	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Hexosaminidase activity (GO:0015929)	p<0.05	1.29E-07	438.747253	8961.63525	*HEXB;HEXA;HEXD;OGA*
Hydrolase activity, Hydrolyzing O-glycosyl compounds (GO:0004553)	p<0.05	0.00000142	170.529915	2956.70059	*CHIT1;NEU3;IDUA;HEXD*
Histone demethylase activity (GO:0032452)	p<0.05	0.01435944	75.0037594	578.210271	*KDM6B;JARID2*
Metal ion binding (GO:0046872)	p<0.05	0.02248459	7.61604697	53.1065356	*ARSA;HSPA5;LPL;HPRT1;SNCA*
Calcium ion binding (GO:0005509)	p<0.05	0.02550827	9.44711538	62.5745064	*ARSA;HSPA5;LPL;SNCA*

Table 4: ChIP-X enrichment analysis for transcription factor enrichment in tay-sachs disease-associated genes

Terms	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
IRF8 27001747 Chip-Seq BMDM Mouse	p<0.05	0.05950828	5.31158379	44.1206454	*KDM6B;NEU3;HHEX;GM2A;HEXB*
SOX2 19030024 ChIP-ChIP MESCs Mouse	p<0.05	0.05950828	7.81542811	63.8120451	*HSPA5;IDUA;GLB1;EIF2AK3;JARID2*
NANOG, 18692474 ChIP-Seq MEFs Mouse	p<0.05	0.05950828	5.18728909	42.2402113	*ARSA;IDUA;GLB1;HEXB;SMPD1*
TCF7 22412390 ChIP-Seq EML Mouse	p<0.05	0.07207674	4.83500264	37.0541278	*KDM6B;SETX;CHIT1;HHEX;NEU4*
NANOG, 18692474 ChIP-Seq MESCs Mouse	p<0.05	0.10636987	4.11840888	29.0405068	*SETX;ARSA;IDUA;GLB1;HEXB*

accumulation occurs specifically within the acidic lysosomal compartment (Lui *et al.,* 2026). The fact that azurophil granules and secretory granules also showed significant enrichment is an interesting finding, as these compartments are primarily associated with neutrophil function and immune cell degranulation. This may suggest that immune cells in TSD patients are also affected by lysosomal enzyme deficiencies, which could contribute to the neuroinflammatory component of disease progression that has been increasingly recognised in lysosomal storage disorders (González-Sánchez *et al.,* 2025).

The enrichment of primary lysosome and lytic vacuole terms alongside the classical lysosomal lumen reflects the multiple stages of lysosomal biogenesis and maturation that are affected when lysosomal hydrolases like Hexosaminidase A are deficient. In TSD, the absence of functional HexA not only prevents substrate clearance but also disrupts the overall functional state of the lysosomal compartment, as uncleared substrates alter luminal pH and membrane stability over time (Leal *et al.,* 2020; Lopshire *et al.,* 2023). Enrichment of molecular function (Table 3) Hexosaminidase activity (GO:0015929) was predominantly represented, with a combined score of 8,961.64 and an odds ratio of 438.75, followed by hydrolase activity (GO:0004553), chitinase activity, acetylglucosaminyltransferase activity, and histone demethylase activity. The latter was represented by KDM6B and JARID2, suggesting epigenetic functions. Among the enriched GO terms were metal ion and calcium ion binding activities, underlining the importance of cofactors in enzymatic reactions. The dominant enrichment of hexosaminidase activity directly validates the known enzymatic basis of Tay-Sachs disease and confirms that the gene set retrieved from DisGeNET is capturing the core disease mechanism (Leal *et al.,* 2020). The identification of histone demethylase activity through KDM6B and JARID2 is a particularly notable finding because it introduces an epigenetic dimension to TSD pathobiology that has not been widely discussed in the context of this disease. KDM6B is a histone H3K27 demethylase known to regulate neuronal differentiation and inflammatory gene expression, and its dysregulation could contribute to altered transcriptional programmes in neurons affected by GM2 accumulation (Rots *et al.,* 2023). The presence of metal ion and calcium ion binding activities among enriched molecular functions is also relevant, as calcium homeostasis is closely linked to lysosomal function and lysosomal membrane integrity (González-Sánchez *et al.,* 2025). The hydrolase activity enrichment represented by CHIT1, NEU3, IDUA and HEXD further confirms the broader hydrolytic enzyme network active in the lysosome, and the presence of IDUA — a gene mutated in Hurler syndrome — among the enriched genes indicates a shared enzymatic landscape with other lysosomal storage disorders, which has implications for the co-disease mapping findings discussed below (González-Sánchez *et al.,* 2025).

Transcription Factor Enrich (Table 4) IRF8, SOX2, and NANOG have been identified as major regulators, providing overall control of gene expression involved in pluripotency, development or immune regulation. Other regulatory components that add complexity to the network are *TCF7, SFPI1, SOX3, OCT4* or *GATA1.* The identification of SOX2 as a major transcriptional regulator of TSD-associated genes is biologically meaningful because SOX2 is a master regulator of neural stem cell identity and neurogenesis. Its involvement here suggests that the transcriptional programmes governing early neuronal development may be disrupted in TSD, potentially explaining the

Table 5: Reactome pathway enrichment analysis for tay-sachs disease-associated genes

Terms	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Glycosphingolipid catabolism	p<0.05	3.68E-16	284.857143	11596.2426	*NEU3;ARSA;NEU4;GM2A;GLB1*
Glycosphingolipid metabolism	p<0.05	9.08E-15	174.236152	6413.59882	*NEU3;ARSA;NEU4;GM2A;GLB1*
Sphingolipid metabolism	p<0.05	1.95E-12	86.9037901	2697.22463	*NEU3;ARSA;NEU4;GM2A;GLB1*
Metabolism of lipids	p<0.05	0.00000383	12.8489305	208.895247	*NEU3;ARSA;NEU4;GM2A;GLB1*
Metabolism	p<0.05	0.00000386	8.21975993	131.720774	*ARSA;IDUA;HEXB;HEXA;LPL*

selective vulnerability of neurons to GM2 accumulation (Hagey *et al.,* 2022). IRF8 is a transcription factor primarily associated with microglial differentiation and immune cell function, and its enrichment points to a possible microglial contribution to TSD neuropathology. NANOG, typically associated with pluripotency maintenance, has also been shown to regulate metabolic gene networks, and its appearance in this analysis may reflect broader gene regulatory disruptions rather than a direct developmental role (González-Sánchez *et al.,* 2025).

The Reactome pathway analysis (Table 5) Confirmed glycosphingolipid catabolism ($p < 0.05$, combined score = 11,596.24) and broader sphingolipid metabolism were central pathways, while involvement of keratan sulfate degradation, sialic acid metabolism, neutrophil degranulation, and lipid metabolism showed systemic metabolic dysregulation. The confirmation of glycosphingolipid catabolism and sphingolipid metabolism as the most significantly enriched Reactome pathways is consistent with the known biochemical basis of TSD and validates the analytical approach used in this study (Ryckman *et al.,* 2020). The additional enrichment of keratan sulfate degradation and neutrophil degranulation pathways is noteworthy, as keratan sulfate is a glycosaminoglycan processed in lysosomes and its accumulation has been reported in related storage disorders, suggesting shared lysosomal degradation bottlenecks. The involvement of neutrophil degranulation pathways further supports the immune-related findings from the cellular component analysis, reinforcing the hypothesis that innate immune dysregulation is a secondary feature of TSD pathophysiology (González-Sánchez *et al.,* 2025; Leal *et al.,* 2020).

Metabolite enrichment identified eleven ganglioside species (HMDB04888–HMDB04898), each associated with *NEU3, NEU4, GM2A, GLB1* and *HEXB* ($p<0.05$, combined score = 33,358.3). These metabolites, which differ in their length of fatty acid chains (C50–C64), underscore a basic disturbance in ganglioside metabolism and can be used as possible biomarkers for disease monitoring and therapeutic assessment. The identification of eleven distinct ganglioside species with high combined enrichment scores provides a molecular fingerprint of the metabolic disturbance in TSD. The fact that these gangliosides span a range of fatty acid chain lengths from C50 to C64 suggests that the enzymatic blockade affects gangliosides of varying structural complexity, not just the most abundant species (Deschenes *et al.,* 2023). This diversity of accumulated substrates may partially explain the heterogeneity of clinical presentation seen across TSD subtypes, as different neuronal populations may preferentially accumulate different ganglioside species. From a translational perspective, the consistent association of all eleven species with *NEU3, NEU4, GM2A, GLB1* and *HEXB* makes them candidates for biomarker development in disease monitoring and for tracking the response to substrate reduction or gene therapy interventions. The range of fatty acid chain lengths also implies that dietary and metabolic factors influencing sphingolipid biosynthesis could modulate the rate of substrate accumulation, which is an aspect worth investigating in future nutritional or metabolic intervention studies in TSD patients (Deschenes *et al.,* 2023).

The bioinformatic enrichment analysis offers new molecular insights into TSD, adding complexity to interactions among lysosomal dysfunction, sphingolipid metabolism, and cellular homeostasis beyond that expected from a classical enzymatic deficiency (González-Sánchez *et al.,* 2025). Six core genes, namely, *GLB1, HEXB, HEXA, GM2A, NEU3* and *NEU4*, involved in ganglioside catabolism support established biochemistry and suggest a coordinated lysosomal glycosphingolipid degradation process (Allende *et al.,* 2023). Significant enrichment of lysosomal and vacuolar lumen localizations underlines trafficking, acidification and enzyme maturation, with unexpected implications for azurophil and secretory granules in neuropathology. Molecular function analysis confirmed hexosaminidase activity and revealed novel epigenetic links via *KDM6B* and *JARID2,* pointing towards potential chromatin dysregulation (Rots *et al.,* 2023).

Transcription factor enrichment of *SOX2, IRF8* and *NANOG* implicates disrupted neuro-developmental programs and immune regulation in disease progression (Hagey *et al.,* 2022). Reactome analysis identified sphingolipid and glycosphingolipid metabolism as important, along with connections to keratan sulfate and neutrophil degranulation, with systemic metabolic involvement. Metabolite analysis identified eleven gangliosides matching core gene functions, emphasizing substrate accumulation as a primary mechanism. Integration of transcriptional, pathway, and metabolite data supports a multilayered model of disease, with possible therapy interventions in the form of transcriptional modulation, anti-inflammatory strategies and epigenetic interventions (Han *et al.,* 2023). Limitations include computational predictions, incomplete

databases, and a gene-centric approach, underlining the need for experimental validation of models using multi-omics approaches in patient-derived materials. The convergence of findings across GO biological processes, cellular components, molecular functions, Reactome pathways, transcription factor networks and metabolite analysis around the same core set of genes — NEU3, NEU4, GM2A, GLB1, HEXB and HEXA — provides a strong multi-platform validation of their central roles in TSD pathogenesis (Allende *et al.,* 2023; González-Sánchez *et al.,* 2025). This kind of cross-analytical consistency is important in bioinformatics studies because it reduces the likelihood that individual enrichment results are artefacts of a single database's annotation bias. The epigenetic findings through KDM6B and JARID2, and the transcription factor findings through SOX2 and IRF8, together suggest that TSD pathology extends beyond the classical enzymatic defect and involves disruption of gene regulatory networks that govern neuronal identity and immune surveillance (Hagey *et al.,* 2022; Rots *et al.,* 2023). Future experimental studies should prioritise validation of these regulatory connections using patient-derived induced pluripotent stem cell models or post-mortem brain tissue from TSD patients, where both the enzymatic and transcriptional abnormalities can be assessed simultaneously.

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