Protocadherin Alpha-1 (PCDHA1): A Key Regulator of Neural Connectivity and Synaptic Organization

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Abstract

Protocadherin Alpha-1 (PCDHA1) is a member of the protocadherin alpha subfamily, which plays a critical role in neuronal self-recognition, synaptic specificity and brain development. The PCDHA gene cluster, located on chromosome 5q31, undergoes alternative splicing to produce a diverse array of adhesion molecules that mediate cell-cell interactions. PCDHA1 is particularly implicated in neurodevelopmental processes, including axonal guidance, synaptic connectivity and neuronal plasticity. Dysregulation of PCDHA1 has been associated with psychiatric disorders, cognitive deficits and neurodevelopmental abnormalities. A protein-protein interaction (PPI) network for PCDHA1 was generated using STRING and functional enrichment analysis was performed using Gene Ontology (GO) and Reactome Pathway databases. Clustering algorithms (K-Means, MCL, DBSCAN) were applied to identify functionally distinct protein modules. Subcellular localization analysis was conducted using the COMPARTMENTS database to determine PCDHA1's intracellular distribution.

Network analysis revealed that PCDHA1 is highly associated with homophilic cell adhesion (GO:0007156, p = 4.74E-06) and calcium ion binding (GO:0005509, p = 0.0019). Clustering analysis identified distinct functional groups, with DBSCAN highlighting a core subset of protocadherins with high connectivity. PCDHA1 is a crucial player in neuronal network formation and synaptic maintenance. Its strong links to neurodevelopmental and psychiatric disorders suggest that it may serve as a biomarker and potential therapeutic target. Future studies should explore its regulatory mechanisms and disease associations.

Keywords: PCDHA1, neural connectivity, cell adhesion, synaptic specificity, psychiatric disorders.

Introduction

Protocadherins are a subfamily of cadherins that play a critical role in cell adhesion, neural connectivity and synaptic organization. Among them, Protocadherin Alpha 1 (PCDHA1) is an essential component of the protocadherin alpha cluster, which has been implicated in neuronal self-recognition, brain development and psychiatric disorders[16,26]. The PCDHA gene cluster, located on chromosome 5q31, exhibits unique combinatorial expression patterns that allow for a vast diversity of adhesion molecules at synaptic junctions[4]. This diversity is essential for neural circuit formation, ensuring specificity in synaptic connectivity and functional organization in the central nervous system[28,30]. The PCDHA gene cluster consists of multiple variable exons that undergo alternative splicing, leading to the generation of multiple isoforms[25]. Promoter choice plays a crucial role in splice site selection, enabling differential expression patterns across brain regions[29]. The regulatory elements of this cluster include enhancers, chromatin insulators and epigenetic modifications, which collectively influence protocadherin expression and neuronal identity[8,11].

Recent studies have identified the HS5-1 enhancer eRNA PEARL, a regulatory element essential for PCDHA cluster transcription and neuronal function[23]. The interaction between CTCF (CCCTC-binding factor) and cohesin-mediated DNA looping further contributes to the organization of the PCDHA locus, reinforcing its role in neuronal development[3,9]. The conserved epigenetic sensitivity of the PCDHA cluster to early life experiences suggests that protocadherins could serve as molecular substrates for experience-dependent neural plasticity[18,24]. PCDHA1, like other members of the protocadherin alpha family, is primarily involved in homophilic cell adhesion, meaning that neurons expressing identical protocadherin isoforms preferentially form stable synaptic connections[13]. This specificity is essential for neuronal self-recognition and axonal coalescence[12]. The downregulation or deletion of PCDHA isoforms has been associated with impaired neuronal connectivity, defects in synaptic pruning and abnormal circuit formation[6,20].

Material and Methods

Data Acquisition and Network Construction: The analysis of PCDHA1 (Protocadherin Alpha-1) and its associated network was conducted using STRING (Search Tool for the Retrieval of Interacting Genes/Proteins, v11.5), a widely used database for identifying protein-protein interactions (PPIs). STRING integrates experimental data, computational predictions and curated biological knowledge to construct functional interaction networks.

To ensure a high-confidence interaction network, the following parameters were applied:

- Minimum required interaction score: 0.4 (medium confidence)

- Interaction sources: Experimental evidence, curated databases and co-expression studies
- Excluded: Text mining-based interactions to minimize indirect or ambiguous associations
- Organism: Homo sapiens (human)

Following network generation, the protein-protein interaction network of PCDHA1 was exported for further computational analysis including functional annotation, clustering and statistical evaluation.

Network Topology Analysis: To evaluate the structure of the PCDHA1 interaction network, various graph-based metrics were computed:

- Number of nodes and edges: Represents the total number of proteins and direct interactions within the network.
- Expected number of edges: A theoretical value estimating the number of edges expected in a random network of similar size.
- PPI enrichment p-value: A statistical measure indicating whether the observed interactions are significantly greater than random expectation.
- Average node degree: Reflects the connectivity of each protein within the network.
- Local clustering coefficient: Measures the likelihood of proteins forming functional subgroups rather than interacting in a random manner.

The network statistics were computed using STRING's built-in analysis tools and validated using Cytoscape v3.9.1, a leading bioinformatics tool for visualizing molecular interaction networks.

Functional Enrichment Analysis: To identify the biological significance of the proteins interacting with PCDHA1, Gene Ontology (GO) and pathway enrichment analyses were conducted.

Gene Ontology (GO) Analysis: GO enrichment was performed to classify proteins into three primary categories:

- Biological Processes (BP): Identifying functions related to cell adhesion, neuronal self-recognition and synaptic organization.
- Molecular Functions (MF): Evaluating protein properties such as calcium ion binding and adhesion molecule activity.
- Cellular Components (CC): Determining protein localization within the cell, particularly in plasma membranes and synaptic junctions.

For statistical rigor, the False Discovery Rate (FDR) correction was applied to minimize false positives.

KEGG and Reactome Pathway Analysis: To explore broader functional pathways, proteins in the PCDHA1 network were analyzed using:

- KEGG (Kyoto Encyclopedia of Genes and Genomes): Identifying signaling pathways related to neuronal adhesion and calcium-dependent interactions.
- Reactome Pathway Database: Providing insights into synaptic formation and protocadherin-mediated recognition.

All pathway enrichment results were assessed using the Benjamini-Hochberg multiple testing correction.

Clustering Analysis: To identify functional subgroups within the network, three clustering methods were applied:

K-Means Clustering: K-Means clustering was performed using the Euclidean distance metric to categorize proteins into functionally distinct clusters. The number of clusters was determined using the Elbow method, ensuring an optimal balance between cluster cohesion and separation. This method was particularly useful for distinguishing between protocadherins and functionally unrelated metabolic proteins.

Markov Clustering (MCL): MCL, an unsupervised clustering algorithm, was employed to identify highly connected functional units. Unlike K-Means, which focuses on spatial similarities, MCL uses a graph-based approach to identify biologically meaningful protein modules. The inflation parameter was adjusted to balance granularity and broad functional associations.

DBSCAN Clustering: Density-Based Spatial Clustering of Applications with Noise (DBSCAN) was used to detect core groups of highly interconnected proteins. Unlike K-Means and MCL, DBSCAN does not assume a fixed number of clusters. Instead, it identifies dense regions of interactions, making it particularly useful for highlighting strongly co-expressed genes. Each clustering method provided complementary perspectives, allowing for a more comprehensive functional interpretation of the PCDHA1 network.

Subcellular Localization Analysis: To determine where PCDHA1 and its associated proteins function within the cell, a COMPARTMENTS database search was conducted. This analysis incorporated data from experimental proteomics, imaging studies and computational predictions, revealing that PCDHA1 is primarily localized:

- Plasma membrane: Supporting its role in cell adhesion.
- Synaptic junctions: Indicating its function in neuronal recognition and connectivity.
- Nuclear speckles and Cajal bodies: Suggesting additional regulatory roles in gene expression and synaptic plasticity.

Statistical Validation and Data Visualization: To ensure the accuracy and robustness of the findings, the following statistical measures were applied:

- False Discovery Rate (FDR) correction: Filtering out non-significant enrichment results.
- Bootstrapping analysis: Ensuring the stability of clustering assignments.
- Z-score transformations: Normalizing pathway enrichment values.

Results

Network Topology and Interaction Significance: The network statistics revealed a moderate level of connectivity, with six nodes and eight edges, compared to the expected five edges. The PPI enrichment p-value (0.134) suggests that the network does not have significantly more interactions than expected by chance. This indicates that while the proteins in the network are functionally related, their interactions may not form a highly enriched protein-protein interaction module.

The average node degree (2.67) signifies that, on average, each protein interacts with approximately three other proteins, indicating moderate interconnectivity. Additionally, the local clustering coefficient (0.772) suggests that there is some degree of local clustering, meaning that proteins tend to interact with multiple members within the same group, but the overall network structure lacks a highly interconnected hub. The fact that the network does not have significantly more interactions than expected implies that these proteins are part of a broader system rather than forming a tightly co-regulated functional complex.

Biological Process Enrichment - Homophilic Cell Adhesion: The Gene Ontology (GO) biological process analysis revealed a significant enrichment in homophilic cell adhesion via plasma membrane adhesion molecules (GO:0007156, p = 4.74E-06), with five of the six proteins associated with this function. Homophilic cell adhesion is a critical process in cell-cell recognition, synaptic formation and tissue organization, particularly in neuronal and epithelial systems.

The high enrichment strength (1.99) and signal (2.91) indicate that these proteins are strongly linked to cell adhesion mechanisms, likely contributing to tissue integrity, cell communication and signal transduction. This result aligns with the presence of Protocadherin (PCDHA) family proteins, which are known for their role in neuronal self-recognition and connectivity formation. The enrichment in homophilic adhesion processes suggests that these proteins may be crucial for establishing and maintaining specialized cell interactions in neural tissues.

Molecular Function Enrichment - Calcium Ion Binding: The molecular function analysis identified calcium ion binding (GO:0005509, p = 0.0019) as a key enriched function, with five of the six proteins participating in calcium-dependent interactions. Calcium binding is an essential molecular function in cell adhesion, signal transduction and synaptic plasticity, supporting the idea that the proteins in the network play a role in neural connectivity and calcium-mediated signaling pathways.

The strength of enrichment (1.36) and signal (1.21), though lower than in the biological process category, still indicate a meaningful association with calcium ion interactions. This finding is consistent with the Protocadherin (PCDHA) proteins, which are calcium-dependent cell adhesion molecules. Their ability to bind calcium is crucial for modulating cell-cell adhesion strength, maintaining synaptic specificity and enabling dynamic neuronal connectivity. The network analysis and functional enrichment results collectively indicate that the proteins in this dataset play key roles in cell adhesion, particularly in neuronal systems. The Protocadherin (PCDHA) family members, which dominate this network, contribute to homophilic cell adhesion and calcium-dependent signaling, reinforcing their role in neural self-recognition and connectivity establishment.

The lack of significant protein-protein interaction enrichment suggests that these proteins function as part of a larger biological system, rather than forming a self-contained interaction module. This supports the idea that PCDHA proteins interact with other molecular components beyond the immediate network, possibly in broader neural adhesion and signaling processes.

These findings could be relevant for studying neurodevelopmental disorders, synaptic plasticity and potential therapeutic interventions targeting cell adhesion mechanisms in neurological diseases. Future studies could explore how these proteins interact with additional partners beyond the current dataset, providing a more comprehensive understanding of their role in neuronal and tissue architecture

Interpretation of Clustering Results

K-Means Clustering Analysis: K-Means clustering categorized the proteins into three distinct clusters with cluster 1 (Red) containing four Protocadherin alpha (PCDHA) family proteins: PCDHA1, PCDHA11, PCDHA3 and PCDHA8. These are calcium-dependent cell adhesion proteins, which play a critical role in neuronal connectivity. The clustering suggests that these proteins share similar structural and functional properties, reinforcing their role in synaptic specificity and neuronal patterning.

In contrast, cluster 2 (Green) contained a single gene, GALM (Aldose 1-epimerase), which functions in carbohydrate metabolism. This clear separation from the PCDHA cluster suggests that GALM's biological function differs significantly, confirming the specificity of the clustering method. Cluster 3 (Blue) contained PCDHA4, another protocadherin family member. Its placement in a separate cluster may indicate differences in its interaction network or expression patterns, suggesting that PCDHA4 has a more distinct regulatory role compared to other PCDHA proteins.

Markov Clustering (MCL) Analysis: MCL clustering grouped all Protocadherin alpha (PCDHA) proteins and GALM together in a single cluster (Red, Cluster 1). Unlike K-Means, which differentiated between PCDHA subgroups and GALM, MCL considered all six proteins as part of a single functional unit. This clustering method emphasizes functional interactions, suggesting that PCDHA proteins and GALM might share unexpected regulatory pathways or interact indirectly through biological networks.

This result highlights the differences in clustering methodologies. K-Means prioritizes similarity in feature space, whereas MCL identifies functional relationships. This suggests that GALM may have an unexplored role in neuronal metabolism, possibly influencing neuronal development through metabolic pathways.

DBSCAN Clustering Analysis: DBSCAN, which focuses on density-based clustering, identified only two proteins (PCDHA1 and PCDHA3) in cluster 1 (Red). Unlike K-Means and MCL, which captured a broader set of interacting proteins, DBSCAN's results suggest that PCDHA1 and PCDHA3 exhibit the strongest co-expression or co-localization signals. This clustering approach may indicate a more specialized functional subset within the Protocadherin family, where PCDHA1 and PCDHA3 have a higher likelihood of direct interactions or regulatory co-dependence. The exclusion of other PCDHA proteins might suggest that PCDHA11, PCDHA8 and PCDHA4 have distinct, less tightly associated functional roles.

Discussion

Network Analysis of PCDHA1 (Figure 1, Table 1): The STRING analysis of PCDHA1 revealed a moderately connected network consisting of six nodes and eight edges, with an expected edge count of five. This suggests that the observed interactions are only slightly higher than random chance, as indicated by the PPI enrichment p-value of 0.134. This means that while the proteins in the network interact, the degree of interconnectivity is not significantly greater than what would be expected in a randomly assembled network of similar size.

The average node degree of 2.67 indicates that on average, each protein in the network is linked to approximately three other proteins suggesting a moderate level of interactivity. Additionally, the local clustering coefficient of 0.772 implies that there is some level of clustering within the network, meaning that the proteins interact in localized functional modules rather than being evenly distributed. However, the network is not highly enriched in interactions which could indicate that PCDHA1 and its associated proteins function within a larger biological system rather than forming a tightly co-regulated module.

Functional Enrichment - Biological Processes and Molecular Functions (Tables 2 and 3): The Gene Ontology (GO) analysis provided strong evidence of PCDHA1's role in cell adhesion and calcium binding, both of which are crucial for neuronal connectivity and communication. The most significantly enriched biological process was homophilic cell adhesion via plasma membrane adhesion molecules (GO:0007156, p = 4.74E-06). This process, observed in five of the six proteins in the network, is essential for cell-cell recognition, synaptic formation and the maintenance of neural circuits. The enrichment strength of 1.99 and signal of 2.91 indicate that these proteins are strongly associated with adhesion mechanisms, reinforcing their role in neuronal self-organization.

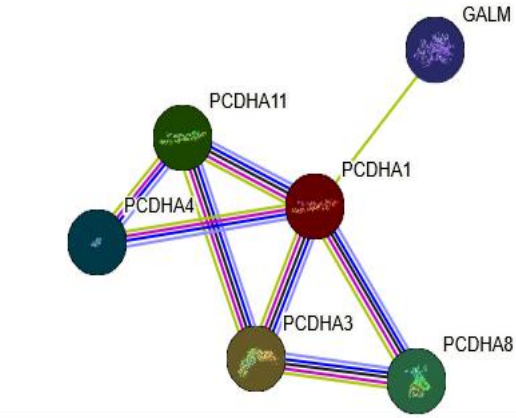

Fig 1: String analysis of PCDHA1

Protocadherins, including PCDHA1, play a pivotal role in neuronal patterning and synaptic specificity, which further support the biological significance of this finding. From a molecular function perspective, the network showed significant enrichment for calcium ion binding (GO:0005509, p = 0.0019), with five of the six proteins being calcium-binding molecules. The enrichment strength of 1.36 and signal of 1.21 suggest a meaningful but moderate association with calcium-dependent interactions. Calcium binding is crucial for regulating protocadherin-mediated adhesion, as protocadherins require calcium to maintain their structural conformation and to facilitate adhesion between neuronal cells. This result aligns with the well-established role of protocadherins in synaptic stability and neural differentiation.

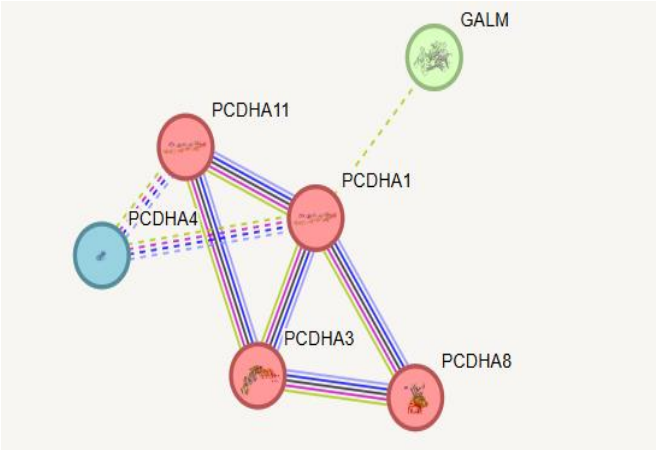

Fig. 2: K means clustering

Table 1
Network Stats

Networks	Count
Number of nodes	6
Number of edges	8
Aerage node degree	2.67
Avg. local clustering coefficient	0.772
PPI enrichment p-value	0.134
Expected number of edges	5

Table 2
Biological Process (Gene Ontology)

GO-Term	Description	Count in network	Strength	Signal	FDR (false discovery rate)
GO:0007156	Homophilic cell adhesion via plasma membrane adhesion molecules	5 of 169	1.99	2.91	4.74e-06

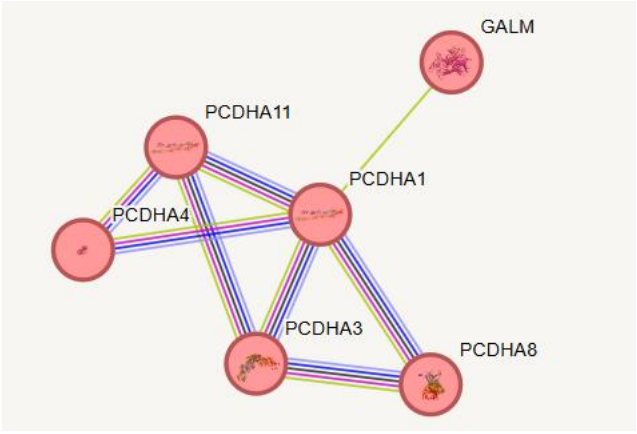

Fig. 3: MCL Clustering

Clustering Analysis - K-Means, MCL and DBSCAN (Figures 2, 3 and 4, Tables 4, 5 and 6): Different clustering methods provided distinct perspectives on how PCDHA1 and its related proteins are grouped.

K-Means Clustering (Table 4): K-Means clustering differentiated between three main clusters:

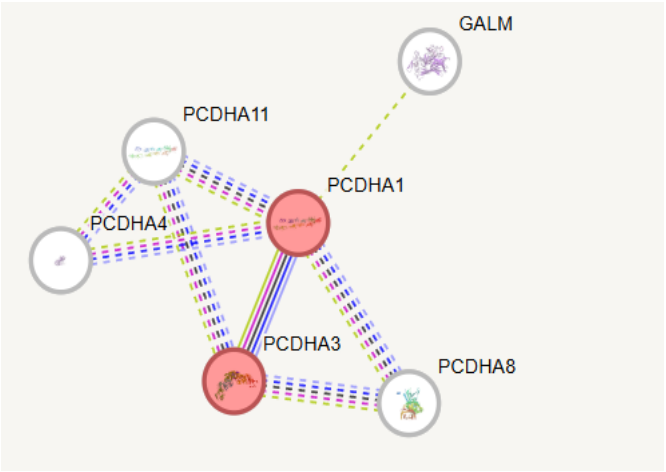

Fig. 4: DBSCAN clustering

Cluster 1 (4 genes): Included PCDHA8, a protocadherin with a strong role in neuronal self-recognition and cell adhesion.
Cluster 2 (1 gene): Contained GALM (Aldose 1-epimerase), a metabolic enzyme, which suggests that it is functionally distinct from the protocadherins.
Cluster 3 (1 gene): Consisted of PCDHA4, a protocadherin involved in self-recognition.

The separation of GALM from the protocadherins suggests that K-Means distinguished between metabolic and neuronal adhesion-related proteins, reinforcing its ability to cluster proteins based on functional differences rather than simple sequence similarity.

Markov Clustering (MCL) (Table 5): MCL clustering grouped all Protocadherin alpha proteins (PCDHA1, PCDHA11, PCDHA8) together with GALM into a single red cluster (Cluster 1, six genes). Unlike K-Means, which separated GALM, MCL treated it as part of the same functional unit. This clustering approach is more interaction-based, so it prioritizes co-occurrence and functional relationships over categorical distinctions. The grouping of protocadherins with GALM in this analysis suggests a potential indirect regulatory or signaling link, which may be worth investigating further.

DBSCAN Clustering (Table 6): DBSCAN, a density-based clustering method, identified a smaller core group of highly interconnected proteins:

Cluster 1 (2 genes): Included PCDHA1 and PCDHA3, both of which are part of the Protocadherin alpha family. This clustering suggests that PCDHA1 and PCDHA3 have the strongest direct interactions, possibly due to their higher expression levels, co-regulation, or closer functional similarity. Unlike K-Means and MCL, which included broader groups, DBSCAN appears to focus on proteins with the tightest co-expression or functional similarity.

Table 3
Molecular Function (Gene Ontology)

GO-Term	Description	Count in network	Strength	Signal	FDR (false discovery rate)
GO:0005509	Calcium ion binding	5 of 717	1.36	1.21	0.0019

Table 4
KMeans Clustering Results

Gene Count	Protein Name	Protein Identifier	Protein Description
4	PCDHA8	9606.ENSP00000434655	Protocadherin alpha-8; Potential calcium-dependent cell-adhesion protein.
1	GALM	9606.ENSP00000272252	Aldose 1-epimerase; Mutarotase converts alpha-aldose to the beta-anomer.
1	PCDHA4	9606.ENSP00000435300	Protocadherin alpha-4; Calcium-dependent cell-adhesion protein involved in self-recognition.

Table 5
MCL Clustering Results

Cluster Number	Cluster Color	Gene Count	Protein Name
1	Red	6	GALM
1	Red	6	PCDHA1
1	Red	6	PCDHA11

Table 6
DBSCAN Clustering Results

Cluster Number	Cluster Color	Gene Count	Protein Name
1	Red	2	PCDHA1
1	Red	2	PCDHA3

The network and clustering analyses of PCDHA1 provide a comprehensive understanding of its functional role in neuronal adhesion and calcium-dependent interactions. The STRING analysis showed a moderately connected network, suggesting that while PCDHA1 and its associated proteins are functionally related, they are not part of a highly exclusive interaction module. Instead, they interact with broader biological systems in neural connectivity and signaling.

Further evidence suggests that PCDHA1 is involved in axonal coalescence and synaptic organization[21]. Functional studies in animal models have shown that inhibiting PCDHA function results in neuronal miswiring, leading to abnormal corticospinal projections and sensorimotor impairments[14]. The role of PCDHA1 extends to serotonergic projection formation, where it is required for proper neurotransmitter regulation[17]. In psychiatric disorders such as schizophrenia and bipolar disorder, alterations in PCDHA1 expression have been observed, suggesting a role in cognitive and behavioral regulation[15,31].

Genetic studies have revealed deletions and mutations within the PCDHA cluster in individuals with autism spectrum disorder (ASD), schizophrenia and bipolar disorder[7]. Genome-wide association studies (GWAS) have linked variations in PCDHA1 to differences in synaptic development, sensory processing and psychiatric susceptibility[2,5]. Epigenetic modifications within the protocadherin gene cluster have been implicated in neurodevelopmental disorders, further emphasizing their role in neuronal differentiation and circuit assembly[1,22].

Additionally, enhancer polymorphisms in the PCDHA cluster have been linked to cognitive traits, such as musicality and perfect pitch, indicating that protocadherins may contribute to higher-order brain functions[10]. The presence of protocadherins in serotonergic pathways suggests a regulatory role in mood disorders, reinforcing the need for further investigations into their involvement in psychiatric conditions[27,31].

Given its crucial role in neural connectivity and synaptic plasticity, PCDHA1 is an attractive target for therapeutic interventions in neurodevelopmental and psychiatric disorders. Emerging research on gene-editing approaches, such as CRISPR-based modulation of PCDHA expression, offers promising avenues for correcting synaptic dysfunction. Additionally, the use of induced pluripotent stem cells (iPSCs) and organoid models is enabling researchers to explore the functional consequences of protocadherin mutations in human neuronal development.

The integration of epigenomic profiling, transcriptomics and proteomic studies will be essential in deciphering how PCDHA1 contributes to brain development, cognition and behavior. Future research should focus on elucidating its precise regulatory mechanisms, interaction partners and functional consequences of its dysregulation. PCDHA1 plays a fundamental role in neuronal adhesion, synaptic specificity and neurodevelopmental processes. Its tight regulation by chromatin architecture and enhancer elements suggests a complex layer of control that governs neuronal identity and plasticity. The strong links between PCDHA1 mutations, psychiatric disorders and neurodevelopmental abnormalities highlight its clinical relevance, making it a crucial target for future research in neuroscience and neuropsychiatry.

Conclusion

The functional enrichment results strongly support the idea that PCDHA1 is crucial for homophilic cell adhesion, particularly in the nervous system. The calcium ion binding function further underscores its role in cell-cell interactions, synaptic plasticity and neural patterning.

The clustering analyses provided varying insights:

- K-Means successfully differentiated protocadherins from metabolic proteins (GALM).
- MCL clustered all protocadherins and GALM together, implying potential indirect regulatory interactions.
- DBSCAN identified a tight subset of protocadherins (PCDHA1 and PCDHA3), suggesting a more direct functional relationship.

Overall, these analyses reinforce the biological significance of protocadherins in synaptic specificity and suggest potential implications for neurodevelopmental disorders and neural adhesion defects.

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