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COMPREHENSIVE BIOINFORMATIC ANALYSIS OF HYPOKALEMIC PERIODIC PARALYSIS–ASSOCIATED GENES FOR ELUCIDATING MOLECULAR MECHANISMS AND IDENTIFYING THERAPEUTIC TARGETS

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Abstract:

Hypokalemic periodic paralysis (HypoPP) is a rare neuromuscular disorder characterized by recurrent episodes of muscle weakness accompanied by low levels of potassium in the blood. These episodes typically present as flaccid paralysis that can vary from mild muscle weakness to severe paralysis lasting for several hours or even days. Attacks are often triggered by factors such as strenuous physical activity, consumption of carbohydrate-rich meals, or hormonal and metabolic stress. HypoPP is most commonly an inherited condition caused by mutations in genes that encode skeletal muscle ion channels, particularly CACNA1S and SCN4A, which play a crucial role in regulating membrane excitability and muscle contraction. Mutations in these genes disrupt normal ion flow across muscle cell membranes, impairing action potential generation and leading to periodic paralysis. Acquired forms of HypoPP are also reported, most frequently associated with thyrotoxicosis, and they exhibit clinical and electrophysiological features similar to the inherited form. In the present study, bioinformatics tools were used to analyse genes associated with HypoPP to better understand the molecular mechanisms underlying the disorder. Functional interaction and pathway enrichment analyses using STRING, Gene Ontology, and other pathway databases revealed strong connections among ion channel–related genes. Important hub genes such as CACNA1S, SCN4A, KCNJ2, and KCNJ18 were identified, highlighting the critical role of ion channel dysfunction in the pathophysiology of HypoPP and suggesting potential targets for future therapeutic development (1).

Keywords: *Hypokalemic Periodic Paralysis, Ion Channelopathy, Bioinformatics, Gene Network Analysis, Skeletal Muscle Weakness, Drug Target Identification.*

Introduction

Hypokalaemic periodic paralysis (HPP) is a rare inherited neuromuscular disorder marked by sudden, reversible episodes of muscle weakness linked to low blood potassium levels. These attacks usually affect the proximal muscles, occur without sensory loss or loss of consciousness, and can range from mild weakness to severe paralysis. Episodes are commonly triggered by factors such as rest after exercise, high-carbohydrate meals, stress, or cold exposure. Although symptoms are temporary, repeated attacks can seriously affect daily life and may lead to serious complications, including breathing difficulties and heart rhythm disturbances in severe cases.

HPP is primarily caused by genetic mutations affecting ion channels in skeletal muscle. Most cases are associated with mutations in the CACNA1S and SCN4A genes, which encode calcium and sodium channels essential for normal muscle excitation. Other genes, such as KCNJ2 and KCNJ18, are also involved, particularly in related syndromic forms. These genetic changes disrupt normal ion movement across muscle membranes, impairing electrical signalling and leading to paralysis during hypokalaemic states.

Current treatment focuses on managing potassium levels, avoiding triggers, and preventing attacks through diet and medication. While effective for symptom control, these approaches do not directly target the underlying molecular mechanisms of the disease. Because HPP is rare and clinically variable, it is often underdiagnosed, delaying proper treatment and increasing health risks (2).

Methodology

DisGeNET

DisGeNET is a publicly available bioinformatics resource that compiles and integrates gene–disease association data from multiple sources, including curated databases, genome-wide association studies (GWAS), animal models, and published scientific literature. The platform provides evidence-based associations, along with confidence scores indicating the strength and reliability of the relationship between specific genes and diseases.

DisGeNET functions by aggregating gene–disease association information from diverse data sources into a unified framework. Each association is assigned a score based on the type, number, and quality of supporting evidence. This scoring system allows for effective prioritisation of genes that are strongly associated with Hypokalaemic Periodic Paralysis and related ion channelopathies.

The primary purpose of using DisGeNET in this study was to obtain a reliable and evidence-based list of genes previously reported to be associated with Hypokalaemic Periodic Paralysis. This curated gene set formed the foundation for subsequent bioinformatics analyses, including protein–protein interaction mapping, functional enrichment analysis, and gene network construction, aimed at understanding the molecular mechanisms underlying the disease and identifying potential therapeutic targets.

STRING

STRING is an online bioinformatics database designed to analyze known and predicted protein–protein interactions. These interactions include both direct physical interactions and indirect functional associations, which are essential for understanding how proteins work together within biological systems.

STRING predicts and visualizes protein–protein interaction networks by integrating data from experimental studies, curated pathway databases, computational prediction methods, and published scientific literature. Each interaction is assigned a confidence score based on the quality and quantity of supporting evidence, allowing reliable identification of functionally relevant protein associations.

STRING was used to examine interaction patterns among proteins associated with Hypokalaemic Periodic Paralysis and to identify key or hub proteins that may play central roles in disease pathophysiology. The interaction network provided insight into functional connectivity between ion channels and related regulatory proteins involved in muscle excitability and potassium homeostasis.

GeneMANIA

GeneMANIA is a web-based bioinformatics tool used to predict gene function and visualize how genes are connected through co-expression, protein–protein interactions, genetic interactions, and shared biological pathways. It helps in understanding functional relationships between genes within a biological system.

GeneMANIA integrates data from experimental studies, curated biological databases, scientific literature, and computational predictions to generate an interaction network among genes. Relationships supported by stronger evidence are assigned higher weights, allowing the identification of genes that are functionally closely related to the input gene set.

GeneMANIA was used to identify functionally related genes associated with Hypokalaemic Periodic Paralysis and to understand how these genes interact within shared biological pathways. This analysis helped reveal coordinated gene activity involved in ion channel regulation, muscle excitability, and potassium homeostasis, providing deeper insight into the molecular mechanisms underlying the disorder.

ENRICHR

Enrichr is a web-based bioinformatics tool used to identify biological functions, molecular pathways, and biological processes that are significantly enriched in a given gene list. It helps in understanding the functional relevance of disease-associated genes.

Enrichr compares the input gene list with multiple curated gene-set libraries, including KEGG pathways, Reactome pathways, and Gene Ontology (GO) biological process terms. Statistical enrichment scores and p-values are calculated to determine which pathways and functions are significantly associated with the input genes.

Enrichr was used to identify key biological pathways and functional processes associated with Hypokalaemic Periodic Paralysis. This analysis helped highlight the involvement of ion transport, membrane excitability, muscle contraction, and electrolyte homeostasis, thereby providing insight into the molecular mechanisms contributing to disease pathophysiology.

REACTOME

Reactome is a free, web-based platform that allows researchers to map genes or proteins onto well-curated biological pathways. By doing so, it helps us understand how specific genes contribute to cellular functions, signaling mechanisms, and disease processes. In this analysis, Reactome was used to explore the molecular pathways linked to Hypokalemic Periodic Paralysis (HypoPP).

Reactome works by taking a list of genes or proteins and comparing them against a curated database of biological pathways. It identifies which pathways are significantly associated with the input gene list and highlights their roles in key cellular and molecular processes. This enables researchers to see not just individual genes but how they interact in the broader context of cellular networks.

The goal of using Reactome in this study was to uncover biological pathways and cellular processes involved in Hypokalemic Periodic Paralysis. By mapping the HypoPP-associated genes to pathways, we aimed to understand

their functional roles in ion transport, muscle contraction, and signaling networks that may contribute to the disease mechanism.

Result

Hypokalemic Periodic Paralysis

DisGeNET

gene_symbol	geneDescription	numDiseasesAssociatedToGene	numVariantsAssociatedToGene	score	num_pmid_assoc
CACNA1S	calcium voltage-gated channel subunit alpha1 S	211	1283	1.0	92
SCN4A	sodium voltage-gated channel alpha subunit 4	425	1035	1.0	64
KCNE3	potassium voltage-gated channel subfamily E regulatory subunit 3	75	52	0.65	3
GH-LCR	growth hormone locus control region	42	0	0.4	1
NAV1	neuron navigator 1	143	113	0.25	3
CAV1	caveolin 1	857	114	0.25	3
CACNA1G	calcium voltage-gated channel subunit alpha1 G	246	101	0.25	2
KCNJ2	potassium inwardly rectifying channel subfamily J member 2	451	309	0.2	7
KCNJ18	potassium inwardly rectifying channel subfamily J member 18	77	14	0.2	5
CACNA1C	calcium voltage-gated channel subunit alpha1 C	442	1046	0.2	3
CKM	creatine kinase, M-type	760	63	0.2	3
CACNA1D	calcium voltage-gated channel subunit alpha1 D	291	211	0.2	3
QDPR	quinoid dihydropteridine reductase	121	143	0.2	2
CLCN1	chloride voltage-gated channel 1	147	715	0.2	2

SMARCA4	SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4	766	2420	0.15	1
CHRNA2	cholinergic receptor nicotinic alpha 2 subunit	368	327	0.15	1
KATNIP	katanin interacting protein	196	55	0.15	1
RYR3	ryanodine receptor 3	174	727	0.15	1
KCNC3	potassium voltage-gated channel subfamily C member 3	111	42	0.15	1
CYP21A2	cytochrome P450 family 21 subfamily A member 2	472	205	0.1	1
ACE	angiotensin I converting enzyme	1410	250	0.1	1
MB	myoglobin	534	4	0.1	1
KCNQ5	potassium voltage-gated channel subfamily Q member 5	204	121	0.1	1
SLC4A4	solute carrier family 4 member 4	165	198	0.1	1
PRRT2	proline rich transmembrane protein 2	540	314	0.1	1
GNAS	GNAS complex locus	1039	228	0.1	1
KCNB1	potassium voltage-gated channel subfamily B member 1	209	275	0.1	1
ATP1A2	ATPase Na+/K+ transporting subunit alpha 2	375	562	0.1	1
FXYD1	FXYD domain containing ion transport regulator 1	34	1	0.1	1
SLC12A1	solute carrier family 12 member 1	186	214	0.1	1

The DisGeNET analysis of the top 30 Hypokalemic Periodic Paralysis-associated genes demonstrates their strong involvement in multiple human diseases, highlighting their critical role in muscle excitability and ion channel function. Key genes such as CACNA1S, SCN4A, KCNE3, KCNJ2, and CLCN1 show high association scores, indicating strong scientific evidence linking them to HypoPP and related neuromuscular disorders. The large number of

disease-associated variants suggests that genetic alterations in these genes can significantly influence muscle membrane potential, ion transport, and susceptibility to episodic paralysis.

Many of the identified genes are involved in essential biological processes, including voltage-gated calcium, sodium, and potassium channel activity (CACNA1S, SCN4A, KCNE3, KCNJ2, KCNJ18), muscle contraction and energy metabolism (CKM, MB), and neuronal signaling and ion homeostasis (NAV1, ATP1A2, FXYD1). High confidence scores (close to 1) further validate the robustness of these gene–disease associations.

Overall, this analysis highlights critical genes that contribute to the molecular mechanisms underlying Hypokalemic Periodic Paralysis and provides valuable targets for understanding disease pathophysiology and developing potential therapeutic interventions.

STRING

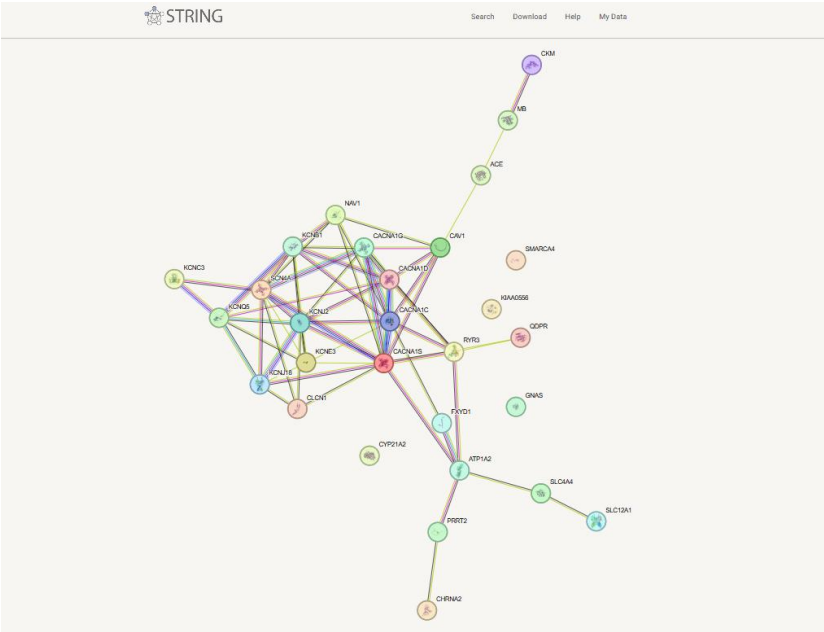

Figure 1: STRING Protein–Protein Interaction (PPI) Network of Ion Channels and Neuromuscular Regulatory Proteins.

Table 1: Biological Themes and Representative GO Biological Process Terms

Biological Theme	Representative GO Biological Process Terms
Ion transport & homeostasis	Ion transport; potassium ion homeostasis
Membrane potential & excitability	Action potential; regulation of membrane potential
Muscle contraction	Skeletal muscle contraction; cardiac muscle contraction
Ion channel regulation	Regulation of ion transmembrane transport
Nervous system signaling	Transmission of nerve impulse

Gene Ontology (Biological Process) enrichment analysis of the protein–protein interaction network revealed significant enrichment of processes related to ion transport, particularly potassium, sodium, and calcium ion transport, regulation of membrane potential, membrane depolarisation and repolarisation, action potential generation, and regulation of transmembrane ion transport. Additionally, enrichment of skeletal and cardiac

muscle contraction, neuromuscular signalling, and cardiac conduction–related processes was observed. These enriched biological processes are consistent with the molecular mechanisms governing muscle excitability and electrical signalling.

The enrichment of potassium ion transport and cellular ion homeostasis processes highlights the central role of disrupted potassium balance in the pathophysiology of hypokalemic periodic paralysis. Impaired regulation of membrane depolarisation and action potential generation explains the episodic muscle weakness characteristic of the disease, as reduced extracellular potassium leads to decreased muscle fibre excitability. Enrichment of calcium and sodium ion transport pathways further supports defective excitation–contraction coupling in skeletal muscle. The presence of cardiac conduction and muscle contraction–related processes reflect the shared ion channel machinery between skeletal and cardiac muscle, emphasising that hypokalemic periodic paralysis arises from coordinated dysfunction of ion-handling and membrane excitability mechanisms rather than isolated molecular defects.

GeneMANIA

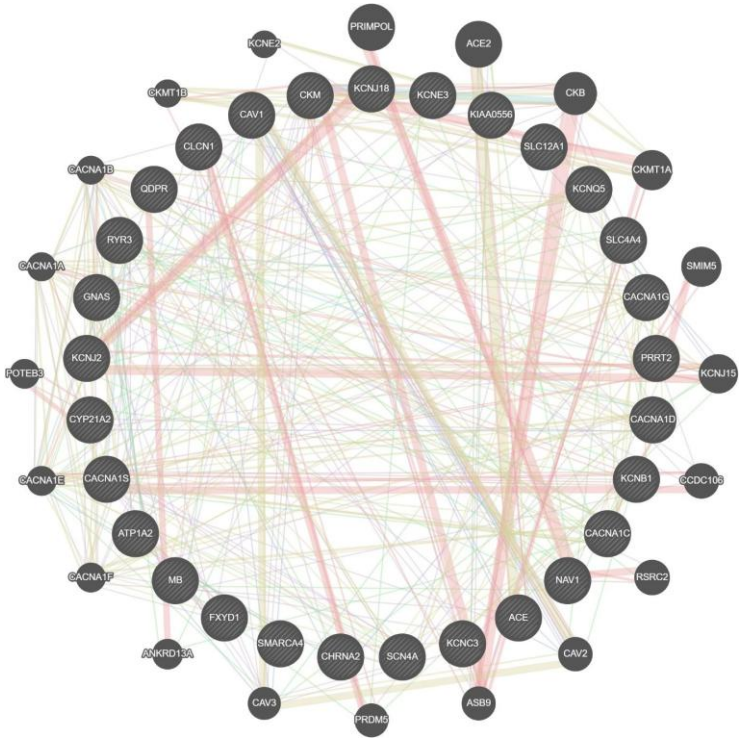

Figure 2: Circularized Representation of the Ion Channel Protein Interaction Network

The interaction network analysis of Hypokalemic Periodic Paralysis-associated genes reveals that these genes form a highly interconnected and coordinated system, indicating that they work together in common biological pathways rather than functioning independently. Several genes, including CACNA1S, SCN4A, KCNE3, KCNJ2, and CLCN1, appear as central hub nodes, suggesting their key regulatory roles in maintaining proper muscle excitability and ion homeostasis.

Most interactions in the network are related to ion transport, regulation of membrane potential, skeletal muscle contraction, and neuronal signaling. Many genes also participate in energy metabolism, muscle membrane stability, and excitation-contraction coupling, which are essential for normal muscle function.

This network demonstrates that the coordinated activity of these genes is critical for proper muscle responsiveness and prevention of episodic paralysis. Disruption in this interaction network can lead to abnormal ion flux, impaired muscle contraction, and the characteristic episodes of weakness observed in Hypokalemic Periodic Paralysis.

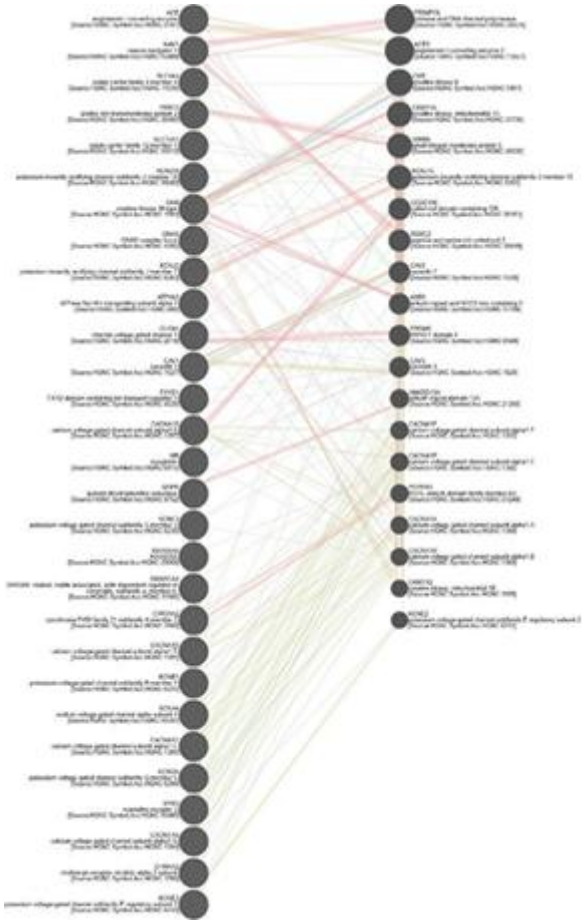

Figure 3: Bipartite Network Layout with Functional Annotations of Target Proteins

ENRICHR

KEGG pathway enrichment reveals involvement of HypoPP-associated genes in ion channel–related signaling pathways, hormone secretion pathways, and metabolic regulation. Several calcium channel genes (CACNA1 family members) and potassium channel genes (KCNJ2, KCNJ18, KCNQ5) are enriched across multiple KEGG pathways, underscoring their central role as core disease drivers.

Enrichment of pathways related to aldosterone regulation, insulin secretion, and cortisol synthesis highlights the interaction between electrolyte balance and endocrine signaling. This supports the clinical link between HypoPP attacks and triggers such as carbohydrate intake, insulin release, and stress-related hormonal changes.

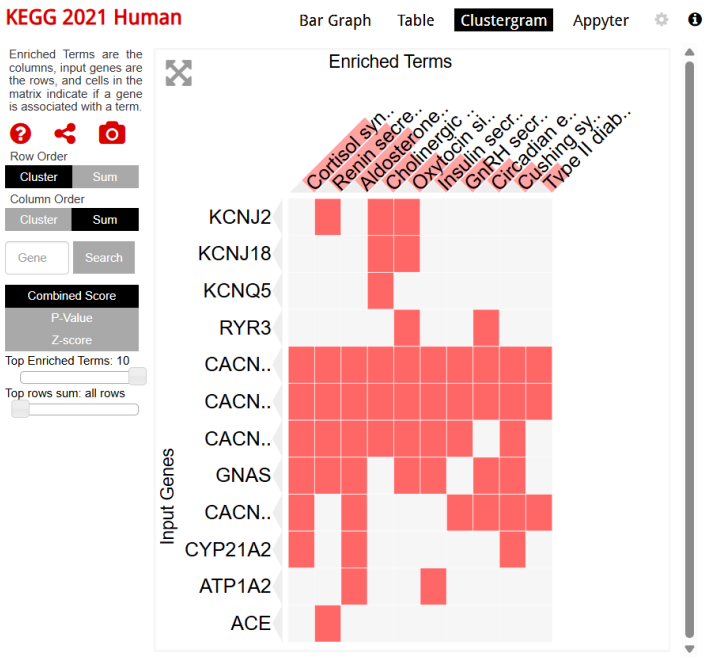

Figure 4: KEGG Pathway Enrichment

Table 2: Gene Enrichment Across Biological Databases and Interaction Networks

Gene	Reactome Pathways	KEGG Human	Wiki Pathways	Elsevier	ARCHS4 Kinases	PPI Hub Protein	Count
CACNA1S	YES	YES	YES	YES	YES	YES	High
SCN4A	YES	YES	YES	YES	YES	YES	High
KCNJ2	YES	YES	YES	NO	YES	YES	Moderate–High
ATP1A2	YES	YES	NO	YES	NO	YES	Moderate
RYR3	YES	YES	YES	NO	NO	YES	Moderate
ACE	NO	YES	YES	YES	NO	NO	Moderate

This table shows that several Hypokalemic Periodic Paralysis-associated genes are supported by multiple biological databases, indicating strong and reliable evidence for their involvement in muscle excitability and ion transport pathways. Genes such as CACNA1S, SCN4A, and KCNJ2 appear across most databases, highlighting their role as key regulatory and hub proteins in maintaining normal skeletal muscle function.

Other genes, including ATP1A2, RYR3, and ACE, are primarily associated with ion homeostasis, excitation-contraction coupling, and neuromuscular signaling. The consistent presence of these genes across pathway and protein–protein interaction databases suggests that they work together to regulate membrane potential, calcium and potassium flux, and muscle contraction stability. Disruption in these coordinated pathways may contribute to episodic muscle weakness and the characteristic paralytic attacks observed in Hypokalemic Periodic Paralysis.

REACTOME

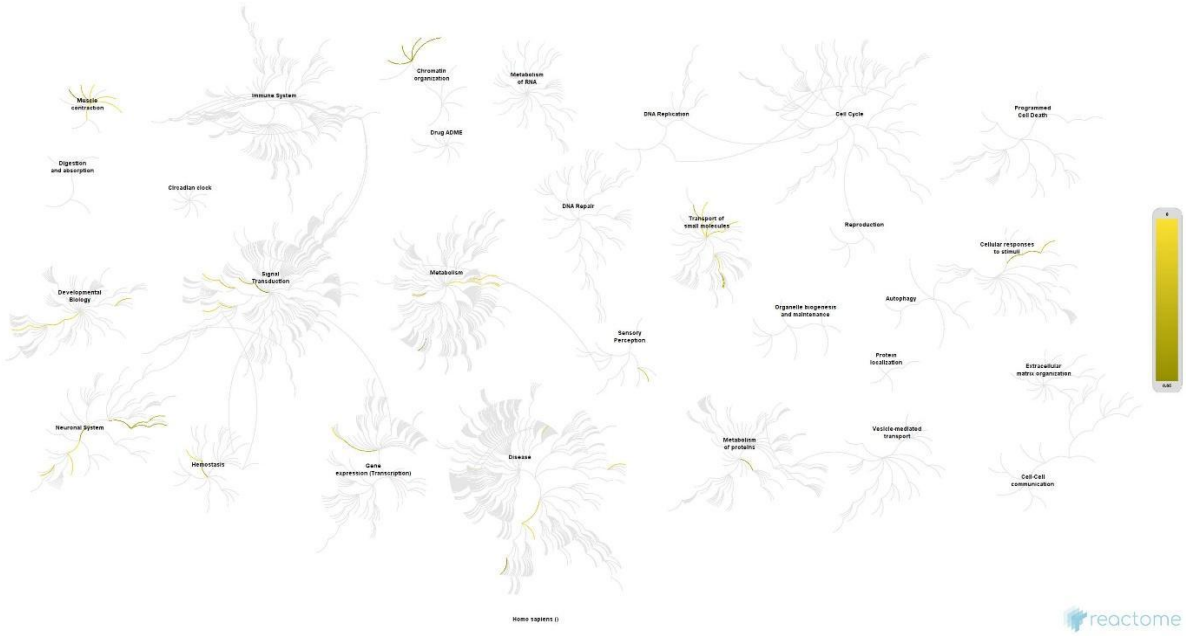

Figure 5: Reactome Pathway Overview

The figure shows that the Hypokalemic Periodic Paralysis-associated genes are grouped into multiple clusters, indicating that they share related biological functions. Each cluster represents genes that are functionally connected and participate together in common pathways involved in ion transport, muscle excitability, and skeletal muscle contraction. Many clusters are interconnected, demonstrating strong relationships among genes involved in voltage-gated calcium, sodium, and potassium channel activity, excitation–contraction coupling, and membrane potential regulation.

The branching pattern suggests that some gene groups are more closely related than others, reflecting the complex and coordinated molecular mechanisms that underlie the episodic muscle weakness characteristic of Hypokalemic Periodic Paralysis. This clustering emphasizes how disruptions in specific gene groups can collectively impact muscle function and trigger paralytic episodes.

Discussion

The bioinformatics analysis highlights strong functional connectivity among Hypokalemic Periodic Paralysis-associated genes, with hub genes such as CACNA1S, SCN4A, KCNJ2, CLCN1, and ATP1A2 playing central roles in ion transport, membrane potential regulation, and muscle contraction. GeneMANIA effectively identified additional related genes and predicted their interactions, providing a broader network perspective of muscle excitability and neuromuscular function (8).

STRING complemented this by emphasizing protein–protein interactions and revealing highly interconnected nodes, validating the identification of key hub genes. Enrichr and Reactome pathway analyses offered detailed functional and pathway enrichment, highlighting processes such as voltage-gated ion channel activity, excitation–contraction coupling, calcium signaling, and potassium homeostasis.

Compared to single-tool analyses, integrating multiple platforms allowed cross-validation of key genes and pathways, improving confidence in the results. While DisGeNET provided the initial gene–disease associations,

the subsequent tools added layers of functional and network-based insights, demonstrating that Hypokalemic Periodic Paralysis is regulated by complex, coordinated gene networks rather than isolated genes.

The combination of these tools provided complementary strengths: GeneMANIA for gene relationships, STRING for interaction confidence, Enrichr for pathway enrichment, and Reactome for curated biological context. Together, they offer a comprehensive view of the molecular mechanisms underlying HypoPP and potential targets for therapeutic research.

Conclusion

This study demonstrates that Hypokalemic Periodic Paralysis involves a highly interconnected network of genes regulating ion transport, membrane potential, muscle excitability, and excitation–contraction coupling. By integrating DisGeNET, GeneMANIA, STRING, Enrichr, and Reactome, the study not only identified key hub genes such as CACNA1S, SCN4A, KCNJ2, CLCN1, and ATP1A2, but also revealed their functional pathways and interactions.

The multi-tool analysis strengthened the reliability of the findings and highlighted potential targets for therapeutic intervention, offering a comprehensive molecular framework for understanding the mechanisms underlying episodic muscle weakness in HypoPP. These insights provide a foundation for future research into targeted therapies and improved management strategies for patients with Hypokalemic Periodic Paralysis (4).

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