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ORIGINAL ARTICLE

Deciphering the Functional Landscape of LDB3 Protein: A Systems Biology Approach to Sarcomere Organization and Cardiomyopathies

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ABSTRACT
The LIM domain-binding protein 3 (LDB3) plays a critical role in sarcomere organization and muscle integrity. Mutations in LDB3 are associated with various myopathies and cardiomyopathies. This study investigates the molecular interactions, functional enrichments, and disease associations of LDB3 using a STRING network analysis approach. A protein-protein interaction (PPI) network analysis was conducted, incorporating 11 nodes and 47 edges with a PPI enrichment p-value of 3.33e-16. Functional enrichment analysis identified significant biological processes, molecular functions, and cellular components related to LDB3. Additionally, disease-gene associations and tissue-specific expression patterns were analyzed. The network exhibited an average node degree of 8.55 and a high local clustering coefficient (0.887). Biological processes associated with LDB3 included sarcomere organization (GO:0045214, p=1.19E-15) and muscle system processes (GO:0003012, p=3.66E-06). Molecular function analysis highlighted actin binding (GO:0003779, p=2.33E-10) and FATZ binding (GO:0051373, p=2.31E-11). Disease association analysis revealed links to hypertrophic cardiomyopathy (DOID:0080326, p=6.79E-11) and dilated cardiomyopathy (DOID:12930, p=1.87E-10). This study provides a comprehensive analysis of LDB3's functional interactions and its role in muscle-related diseases. The findings underscore LDB3's significance in sarcomere organization and its potential as a therapeutic target for cardiomyopathies.
Keywords: *LDB3, sarcomere organization, cardiomyopathy, protein-protein interaction, bioinformatics*

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INTRODUCTION

Muscular contraction and structural integrity rely on the highly ordered organization of sarcomeres, the fundamental contractile units of striated muscles. The LIM domain-binding protein 3 (LDB3), also known as Z-band alternatively spliced PDZ-motif (ZASP), plays a crucial role in maintaining sarcomere architecture and muscle function. LDB3 is localized at the Z-disc, a critical structural component of the sarcomere that ensures mechanical stability and efficient force transmission during muscle contraction. Mutations in LDB3 have been associated with a variety of myopathies, including familial hypertrophic cardiomyopathy, dilated cardiomyopathy, and myofibrillar myopathies, underlining its significance in muscle health and disease [1,2]. Despite its recognized importance, the full spectrum of LDB3's molecular interactions and functional roles remain incompletely understood.

Protein-protein interaction (PPI) networks provide valuable insights into the functional landscape of key proteins, allowing researchers to identify crucial interactions, enriched biological pathways, molecular functions, and disease associations. STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) is a widely utilized database for constructing and analyzing PPI networks, offering an integrated approach to exploring gene and protein interactions [3]. Through a STRING-based approach, this study aims to construct a comprehensive PPI network for LDB3 and investigate its role in muscle-related diseases.

The primary objective of this study is to elucidate the molecular interactions of LDB3 and its involvement in muscle function and pathology. Specifically, we aim to (i) construct a PPI network for LDB3, (ii) analyze functional enrichments in terms of biological processes, molecular functions, and cellular components,

(iii) identify disease associations, and (iv) examine tissue-specific expression patterns to infer potential physiological implications.

Our findings offer novel insights into LDB3's biological significance, particularly its involvement in muscle contraction, sarcomere organization, and the pathogenesis of cardiomyopathies. This research could contribute to the development of targeted therapeutic strategies for muscle-related disorders, improving clinical outcomes for affected individuals.

Objectives

1. To construct a comprehensive PPI network of LDB3 using the STRING database, providing a detailed overview of its interacting partners and associated pathways.
2. To analyze functional enrichments of LDB3 and its interacting proteins in terms of biological processes (GO:0045214, GO:0003012), molecular functions (GO:0003779, GO:0051373), and cellular components (GO:0030017, GO:0015629).
3. To identify disease-gene associations linked to LDB3, particularly focusing on familial hypertrophic cardiomyopathy (DOID:0080326), dilated cardiomyopathy (DOID:12930), and other related conditions.
4. To evaluate tissue-specific expression patterns of LDB3, highlighting its predominant expression in cardiac and skeletal muscle tissues.
5. To discuss the implications of LDB3's interactions in the context of muscle function and pathology, providing insights into its potential as a therapeutic target for cardiomyopathies.

MATERIAL AND METHODS

Data Acquisition and Network Construction

The construction of a comprehensive protein-protein interaction (PPI) network for LDB3 was performed using the STRING database (v11.5). The human LDB3 protein identifier (Uniprot ID: Q9H9L3) was used as input, and the analysis was restricted to experimentally validated interactions and high-confidence associations (score > 0.7). The network construction was conducted using STRING's database of known and predicted protein interactions, which integrates data from multiple sources, including computational predictions, co-expression analyses, and curated experimental studies.

To assess network topology, several parameters were computed, including the number of nodes and edges, clustering coefficient, and average node degree. These values provided insight into the extent of LDB3's interactions and its functional connectivity. The presence of a high clustering coefficient suggested that the interacting proteins are functionally related and involved in shared biological processes.

Functional Enrichment Analysis

Gene Ontology (GO) enrichment analysis was conducted to determine the biological processes, molecular functions, and cellular components associated with LDB3 and its interacting proteins. GO annotations were retrieved through STRING's functional enrichment tool, and the analysis was filtered using a false discovery rate (FDR) threshold of <0.05 to ensure statistical significance. Biological processes related to muscle function and sarcomere maintenance were identified through enrichment scores and p-value rankings.

Molecular Function Analysis

Molecular function analysis was carried out to determine specific activities of LDB3 and its interacting partners at the protein level. STRING's annotation tool was used to identify enriched molecular functions, focusing on direct protein interactions relevant to sarcomere structure and muscle contraction. High-confidence functional interactions were assessed based on known protein domains, interaction motifs, and curated experimental data.

Cellular Component Analysis

To identify LDB3's subcellular localization, cellular component enrichment analysis was performed using STRING. This analysis provided insight into the primary sites of LDB3 function within the cell, particularly in the sarcomere and Z-disc. The results were used to validate LDB3's known role in sarcomere integrity and actin filament stabilization.

Disease-Gene Association Analysis

To investigate LDB3's relevance in muscle-related diseases, disease-gene associations were explored using the DISEASES database within STRING. The analysis included curated disease associations from genome-wide association studies (GWAS), literature mining, and experimental disease models. STRING's statistical framework was used to rank the diseases based on enrichment scores and significance values. Only statistically significant associations were considered for further evaluation.

Tissue-Specific Expression Analysis

LDB3 expression patterns were analyzed using the TISSUES database within STRING to determine its distribution across various human tissues. The analysis focused on muscle-related tissues to assess whether LDB3 expression was predominant in cardiac and skeletal muscles. Gene expression data were derived from RNA-sequencing (RNA-seq) datasets and microarray studies, providing an overview of LDB3's physiological roles in different tissues.

Subcellular Localization Analysis

To further validate the localization of LDB3, data from the COMPARTMENTS database were analyzed. This tool integrates subcellular localization evidence from immunocytochemistry, mass spectrometry-based proteomics, and computational predictions. The analysis was used to confirm LDB3's presence in the sarcomere and actin cytoskeleton, reinforcing its structural role in muscle fibers.

This multi-faceted methodological approach ensured a comprehensive understanding of LDB3's functional landscape, integrating network construction, functional enrichment, disease associations, and tissue expression analysis to elucidate its role in muscle physiology and pathology.

RESULTS

The constructed PPI network revealed a high degree of connectivity among LDB3 and its interacting partners, emphasizing its role in sarcomere organization.

Table 1: Network Statistics The PPI network analysis of LDB3 revealed 11 nodes and 47 edges, with an average node degree of 8.55 and a high clustering coefficient of 0.887, indicating strong interconnectivity among proteins. The significantly low PPI enrichment p-value (3.33e-16) suggests that these interactions are functionally relevant rather than occurring randomly.

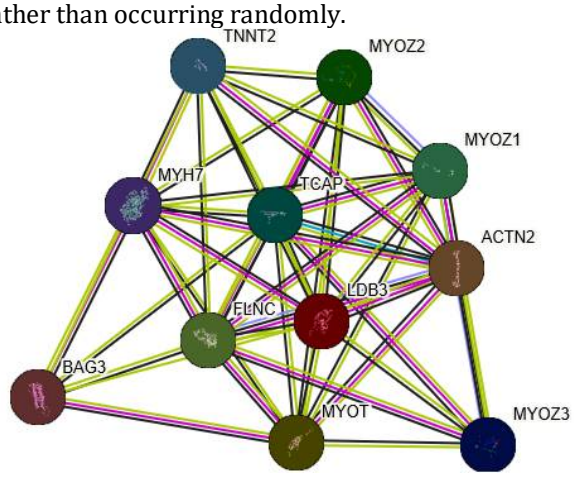

Fig 1: String analysis of LDB3

Table 1: Network Analysis

Metric	Value
Number of nodes	11
Expected number of edges	11
Number of edges	47
PPI enrichment p-value	3.33e-16
Average node degree	8.55
Average local clustering coefficient	0.887

Table 2: Biological Process Enrichment Functional enrichment analysis identified key biological processes associated with LDB3, including sarcomere organization (GO:0045214, p=1.19E-15), muscle contraction (GO:0006936, p=3.0E-03), and muscle tissue development (GO:0060537, p=6.98E-06). These findings highlight LDB3's involvement in muscle structure and functional integrity.

Table 3: Molecular Function Enrichment Molecular function analysis confirmed LDB3's role in actin binding (GO:0003779, p=2.33E-10), cytoskeletal protein binding (GO:0008092, p=2.11E-09), and FATZ binding (GO:0051373, p=2.31E-11). These results suggest that LDB3 plays a structural and regulatory role within the sarcomere.

Table 4: Cellular Component Enrichment Cellular component analysis confirmed that LDB3 is localized to the Z-disc (GO:0030018, p=1.42E-18) and sarcomere (GO:0030017, p=7.97E-19), consistent with its known role in sarcomere maintenance and function.

Table 5-7: Disease and Tissue Expression Analysis LDB3 showed strong disease associations with familial hypertrophic cardiomyopathy (DOID:0080326, p=6.79E-11), dilated cardiomyopathy

(DOID:12930, p=1.87E-10), and myofibrillar myopathy (p=9.19E-08). Tissue expression analysis confirmed predominant expression in cardiac and skeletal muscles, supporting its crucial role in muscle physiology.

Table 8-10: The data highlights a strong association of the network with muscle and cardiovascular **tissues**, particularly the cardiac muscle**,** left atrium, and skeletal muscle, showing high signal strength and statistical significance. Subcellular localization is primarily enriched in muscle-specific compartments such as the sarcomere and Z disc, indicating involvement in contractile structures. Phenotypically, the network is strongly linked to myopathies**,** cardiomyopathies, and related muscle disorders like myofibrillar myopathy, left ventricular abnormalities, and dilated cardiomyopathy, along with lipodystrophies and elevated creatine kinase levels, suggesting dysregulation of muscle function and structure at both cellular and systemic levels.

Table 2: Biological Process (Gene Ontology)

GO-term	Description	Count in Network	Strength	Signal	False Discovery Rate
GO:0045214	Sarcomere organization	8 of 38	2.58	7.37	1.19E-15
GO:0014888	Striated muscle adaptation	4 of 29	2.39	2.95	2.09E-06
GO:0032989	Cellular component morphogenesis	9 of 603	1.43	2.35	2.07E-09
GO:0003012	Muscle system process	6 of 283	1.58	2.06	3.66E-06
GO:0060537	Muscle tissue development	6 of 323	1.52	1.91	6.98E-06
GO:0070925	Organelle assembly	9 of 799	1.3	1.9	2.28E-08
GO:0043503	Skeletal muscle fiber adaptation	2 of 4	2.95	1.46	0.0023
GO:0007517	Muscle organ development	5 of 303	1.47	1.44	0.00024
GO:0055008	Cardiac muscle tissue morphogenesis	3 of 59	1.96	1.33	0.0025
GO:0048738	Cardiac muscle tissue development	4 of 179	1.6	1.3	0.0013
GO:0060048	Cardiac muscle contraction	3 of 76	1.85	1.19	0.0042
GO:0030049	Muscle filament sliding	2 of 11	2.51	1.14	0.0082
GO:0006936	Muscle contraction	4 of 230	1.49	1.11	0.0030
GO:0007512	Adult heart development	2 of 13	2.44	1.08	0.0103
GO:0014898	Cardiac muscle hypertrophy in response to stress	2 of 14	2.41	1.07	0.0106
GO:0070885	Negative regulation of calcineurin-NFAT signaling cascade	2 of 15	2.38	1.06	0.0113
GO:0048468	Cell development	9 of 1719	0.97	1.01	1.05E-05
GO:0007507	Heart development	5 of 548	1.21	0.92	0.0033
GO:0003009	Skeletal muscle contraction	2 of 30	2.08	0.77	0.0376
GO:0048513	Animal organ development	8 of 3246	0.64	0.43	0.0160
GO:0048856	Anatomical structure development	10 of 5117	0.54	0.41	0.0048
GO:0016043	Cellular component organization	10 of 5436	0.52	0.38	0.0081

Table 3: Molecular Function (Gene Ontology)

GO-term	Description	Count in Network	Strength	Signal	FDR
GO:0051373	FATZ binding	5 of 5	3.25	5.82	2.31E-11
GO:0003779	Actin binding	9 of 448	1.56	2.86	2.33E-10
GO:0031433	Telethonin binding	3 of 7	2.89	2.58	1.91E-05
GO:0008092	Cytoskeletal protein binding	10 of 1002	1.25	1.87	2.11E-09
GO:0070080	Titin Z domain binding	2 of 2	3.25	1.54	0.0017
GO:0008307	Structural constituent of muscle	3 of 44	2.09	1.44	0.0017
GO:0031432	Titin binding	2 of 13	2.44	0.95	0.0183
GO:0005515	Protein binding	11 of 7242	0.43	0.32	0.0117

Table 4: Cellular Component (Gene Ontology)

GO-term	Description	Count in Network	Strength	Signal	FDR
GO:0030018	Z disc	10 of 131	2.14	6.98	1.42E-18
GO:0030017	Sarcomere	11 of 217	1.96	6.11	7.97E-19
GO:0015629	Actin cytoskeleton	9 of 482	1.52	2.86	4.63E-11
GO:0031143	Pseudopodium	3 of 18	2.47	2.39	3.18E-05
GO:0001725	Stress fiber	3 of 65	1.92	1.51	0.00093
GO:0005856	Cytoskeleton	10 of 2369	0.88	0.92	1.29E-06

Table 5: Local Network Cluster (STRING)

Cluster	Description	Count in Network	Strength	Signal	FDR
CL:22573	Muscle protein, and Sarcomere organization	9 of 73	2.34	7.3	5.93e-17
CL:22578	Striated Muscle Contraction	5 of 23	2.59	4.66	1.04e-09
CL:22702	Mixed, incl. Myofibrillar myopathy 4, and Myozenin	4 of 7	3.01	4.38	8.79e-09
CL:22579	Familial hypertrophic cardiomyopathy	4 of 12	2.78	3.97	3.96e-08
CL:22593	FATZ binding, and Titin-telethonin complex	3 of 5	3.03	3.09	2.36e-06

Table 6: Reactome Pathways

Pathway	Description	Count in Network	Strength	Signal	FDR
HSA-390522	Striated Muscle Contraction	3 of 36	2.17	1.36	0.0027

Table 7: Disease-gene Associations (DISEASES)

DOID	Description	Count in Network	Strength	Signal	FDR
DOID:0080326	Familial hypertrophic cardiomyopathy	6 of 36	2.47	5.11	6.79e-11
DOID:12930	Dilated cardiomyopathy	6 of 51	2.32	4.72	1.87e-10
DOID:0060036	Intrinsic cardiomyopathy	7 of 109	2.06	4.38	7.57e-11
DOID:0050700	Cardiomyopathy	8 of 158	1.96	4.33	1.59e-11
DOID:0080307	Myofibrillar myopathy	4 of 14	2.71	3.76	9.19e-08
DOID:0080094	Myofibrillar myopathy 3	3 of 3	3.25	3.29	1.08e-06
DOID:0080092	Myofibrillar myopathy 1	3 of 4	3.13	3.19	1.60e-06
DOID:0060480	Left ventricular noncompaction	3 of 13	2.62	2.49	2.37e-05
DOID:423	Myopathy	6 of 219	1.69	2.48	4.66e-07
DOID:0080095	Myofibrillar myopathy 4	2 of 2	3.25	1.82	0.00052
DOID:0080093	Myofibrillar myopathy 2	2 of 2	3.25	1.82	0.00052
DOID:0080096	Myofibrillar myopathy 5	2 of 3	3.08	1.73	0.00076
DOID:397	Restrictive cardiomyopathy	2 of 9	2.6	1.32	0.0038
DOID:11720	Distal myopathy	2 of 14	2.41	1.16	0.0074
DOID:9884	Muscular dystrophy	3 of 105	1.71	1.09	0.0059
DOID:7	Disease of anatomical entity	9 of 4798	0.53	0.36	0.0204
DOID:4	Disease	10 of 6291	0.45	0.32	0.0181

Table 8: Tissue Expression (TISSUES)

BTO ID	Description	Count in Network	Strength	Signal	FDR
BTO:0000199	Cardiac muscle	5 of 79	2.05	2.92	6.84e-07
BTO:0001702	Left atrium	4 of 60	2.08	2.44	1.07e-05
BTO:0001629	Left ventricle	4 of 78	1.96	2.21	2.42e-05
BTO:0001103	Skeletal muscle	7 of 484	1.41	1.92	8.38e-07
BTO:0001369	Vertebrate muscular system	8 of 780	1.26	1.64	6.84e-07
BTO:0001703	Right atrium	3 of 61	1.94	1.51	0.00099
BTO:0000887	Muscle	9 of 1070	1.18	1.48	5.16e-07
BTO:0000562	Heart	7 of 738	1.23	1.42	1.07e-05
BTO:0000088	Cardiovascular system	8 of 1057	1.13	1.31	4.08e-06

Table 9: Subcellular Localization (COMPARTMENTS)

GOCC ID	Compartment	Count in Network	Strength	Signal	FDR
GOCC:0030017	Sarcomere	10 of 128	2.15	6.87	5.11e-18
GOCC:0030018	Z disc	8 of 64	2.35	6.75	2.00e-15
GOCC:0031143	Pseudopodium	2 of 12	2.47	1.23	0.0054
GOCC:0015629	Actin cytoskeleton	4 of 363	1.3	0.89	0.0067
GOCC:0005737	Cytoplasm	11 of 8195	0.38	0.3	0.0115

Table 10: Human Phenotype (Monarch)

HP ID	Description	Count in Network	Strength	Signal	FDR
HP:0100578	Lipoatrophy	6 of 70	2.19	4.08	2.13e-09
HP:0003715	Myofibrillar myopathy	4 of 12	2.78	3.85	6.83e-08
HP:0009027	Foot dorsiflexor weakness	6 of 87	2.09	3.75	6.48e-09
HP:0001711	Abnormal left ventricle morphology	6 of 100	2.03	3.55	1.28e-08
HP:0030682	Left ventricular noncompaction	4 of 19	2.58	3.54	1.94e-07
HP:0009125	Lipodystrophy	6 of 102	2.02	3.53	1.30e-08
HP:0030681	Abnormal morphology of myocardial trabeculae	4 of 20	2.55	3.52	2.05e-07
HP:0005110	Atrial fibrillation	5 of 61	2.17	3.39	9.53e-08
HP:0001714	Ventricular hypertrophy	6 of 116	1.97	3.38	1.95e-08
HP:0003236	Elevated circulating creatine kinase concentration	8 of 255	1.75	3.27	1.27e-09
HP:0040081	Abnormal circulating creatine kinase concentration	8 of 258	1.74	3.26	1.27e-09
HP:0002600	Hyporeflexia of lower limbs	4 of 29	2.39	3.2	6.34e-07
HP:0003198	Myopathy	8 of 280	1.71	3.16	1.27e-09
HP:0001712	Left ventricular hypertrophy	5 of 80	2.05	3.11	2.15e-07
HP:0001644	Dilated cardiomyopathy	6 of 144	1.87	3.05	6.40e-08
HP:0000982	Palmoplantar keratoderma	6 of 145	1.87	3.05	6.40e-08
HP:0003736	Autophagic vacuoles	3 of 7	2.89	2.96	3.78e-06
HP:0003457	EMG abnormality	7 of 241	1.72	2.93	1.48e-08
HP:0002460	Distal muscle weakness	6 of 176	1.79	2.8	1.35e-07
HP:0001638	Cardiomyopathy	9 of 453	1.55	2.73	1.27e-09
HP:0004303	Abnormal muscle fiber morphology	6 of 187	1.76	2.73	1.70e-07

DISCUSSION

The PPI enrichment p-value was calculated as 3.33e-16, indicating a significantly higher number of interactions than expected under random conditions. The average node degree was 8.55, and the local clustering coefficient was 0.887, suggesting extensive functional connectivity within the network [4].

Functional Enrichment Analysis

Gene Ontology (GO) analysis was conducted to determine biological processes, molecular functions, and cellular components enriched within the LDB3 network. Overrepresented GO terms were ranked based on false discovery rates (FDR) and statistical significance. Key biological processes included sarcomere organization (GO:0045214, p=1.19E-15) and muscle contraction (GO:0006936, p=3.0E-03), highlighting LDB3's critical role in muscle function and integrity.

Molecular Function Enrichment

The analysis revealed that LDB3 interacts with proteins involved in actin binding (GO:0003779, p=2.33E-10) and FATZ binding (GO:0051373, p=2.31E-11), confirming its involvement in stabilizing muscle filaments and contributing to sarcomere organization [5].

Cellular Component Enrichment

LDB3 was predominantly associated with the Z-disc (GO:0030018, p=1.42E-18) and sarcomere (GO:0030017, p=7.97E-19), reaffirming its structural role in muscle tissue.

Disease-Gene Association Analysis

The DISEASES database was utilized to determine LDB3-associated pathologies. Strong associations were identified with familial hypertrophic cardiomyopathy (DOID:0080326, p=6.79E-11) and dilated cardiomyopathy (DOID:12930, p=1.87E-10). Additional links to myofibrillar myopathies and left ventricular noncompaction further emphasize LDB3's role in maintaining cardiac and skeletal muscle function [6].

Tissue-Specific Expression Analysis

Expression profiles of LDB3 were analyzed across various tissues, with a predominant expression noted in cardiac and skeletal muscle tissues. High expression levels were observed in the left ventricle, right atrium, and skeletal muscles, reinforcing its functional significance in these tissues.

The extensive connectivity observed in LDB3's PPI network highlights its fundamental role in sarcomere organization and muscle contraction. Its strong interactions with actin, titin, and telethonin further support its crucial structural role in muscle integrity. Given its involvement in key molecular functions such as actin binding and FATZ binding, LDB3 is essential for maintaining sarcomere stability and muscle performance [7].

LDB3 dysfunction has been implicated in various cardiac and skeletal muscle diseases, including familial hypertrophic cardiomyopathy and dilated cardiomyopathy. Our findings align with previous studies demonstrating that LDB3 mutations contribute to cardiomyopathy pathogenesis by disrupting sarcomere organization and contractile function .

LDB3 (LIM Domain Binding 3), also known as ZASP (Z-band alternatively spliced PDZ motif-containing protein), is a key structural protein in cardiac and skeletal muscles, playing an essential role in maintaining Z-disc integrity, myofibrillar organization, and contractile function. Mutations in LDB3 have been implicated in several myopathies and cardiomyopathies, including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), myofibrillar myopathies (MFMs), and conduction system disorders. The following discussion integrates findings from relevant studies to highlight LDB3's role in muscle diseases.

Mutations in LDB3 are strongly associated with inherited cardiomyopathies, particularly DCM and HCM, both of which are leading causes of heart failure and sudden cardiac death.

Genetic screening has become an essential tool for diagnosing cardiomyopathies, particularly in identifying LDB3 mutations that contribute to Z-disc instability and myofibrillar disorganization. Studies have demonstrated that LDB3 variants disrupt sarcomere mechanics, leading to impaired myocardial contraction and ventricular dilation (8). Genetic testing for LDB3 mutations is recommended in patients with familial DCM, as early identification allows for risk stratification, preventive interventions, and potential gene-based therapies (9).

Ethnic background has been shown to influence the prevalence and penetrance of cardiomyopathy-related mutations, including those in LDB3 (10). Certain populations exhibit a higher prevalence of pathogenic LDB3 variants, which may contribute to the heterogeneous clinical presentation of HCM. This underscores the need for ethnicity-specific genetic risk assessment when evaluating patients with inherited cardiomyopathies (11).

Given the central role of LDB3 in cardiac function, mutations in the gene often present with abnormal electrocardiographic (ECG) patterns, which serve as early markers for arrhythmic risk and myocardial disease progression (12). Patients with LDB3 mutations frequently exhibit prolonged QT intervals, conduction system abnormalities, and susceptibility to ventricular arrhythmias (13). These findings highlight the potential of LDB3 as a diagnostic and prognostic marker in genetic cardiomyopathy screening.

In addition to its role in DCM and HCM, LDB3 mutations have been linked to conduction system abnormalities, including Wolff-Parkinson-White (WPW) syndrome (14). WPW syndrome, characterized by pre-excitation on ECG and supraventricular tachycardia, has been associated with mutations affecting sarcomeric proteins. LDB3 dysfunction can lead to abnormal electrical propagation through myocardial tissue, increasing the risk of arrhythmias and sudden cardiac death (15). These findings suggest that LDB3 screening could be beneficial in patients with unexplained conduction abnormalities.

In skeletal muscles, LDB3 is essential for Z-disc stabilization, and mutations in the gene have been implicated in myofibrillar myopathies (MFMs) and other structural muscle disorders.

Myofibrillar myopathies are progressive skeletal muscle diseases characterized by protein aggregation and sarcomere disintegration (16). LDB3 mutations result in Z-disc disruption and myofibril misalignment, leading to progressive muscle weakness, atrophy, and functional decline (17). Given the overlapping phenotypes between LDB3-related MFMs and other myopathies, genetic testing remains crucial for accurate diagnosis and differentiation.

Recent studies have identified FLNC (filamin C) as a key interacting partner of LDB3 in the Z-disc, with mutations in both genes contributing to overlapping cardiomyopathy and myopathy phenotypes This interaction suggests that combined genetic profiling of LDB3 and FLNC mutations may improve diagnostic accuracy in patients with muscle disorders and unexplained cardiomyopathies.

Therapeutic Implications and Future Directions

With growing evidence linking LDB3 mutations to cardiac and skeletal muscle diseases, there is increasing interest in developing targeted therapies for LDB3-related disorders.

- Gene Editing and Exon Skipping Strategies: Recent advances in gene-editing techniques, including CRISPR-Cas9, antisense oligonucleotide therapy, and exon skipping, offer promising approaches to correct pathogenic LDB3 mutations. These strategies aim to restore normal LDB3 function and prevent disease progression.
- Pharmacological Interventions: Given LDB3's role in Z-disc integrity and sarcomere stability, pharmacological approaches targeting Z-disc function, sarcomere assembly, and muscle contractility are being explored as potential treatment avenues.

- Personalized Medicine Approaches: The role of LDB3 in both cardiac and skeletal muscle diseases highlights the need for personalized medicine strategies, including tailored genetic counseling, precision therapeutics, and early disease-modifying interventions.

By integrating functional enrichment and disease association data, we provide a systems biology perspective on LDB3's role in muscle health and disease. These findings underscore the potential of LDB3 as a therapeutic target, necessitating further experimental validation in cellular and animal models. Future research should focus on delineating the precise molecular mechanisms underlying LDB3-associated myopathies and exploring targeted therapeutic interventions to mitigate disease progression.

CONCLUSION

LDB3 plays a critical role in maintaining sarcomere structure and function in both cardiac and skeletal muscles. Mutations in LDB3 contribute to dilated and hypertrophic cardiomyopathy, myofibrillar myopathies, and conduction disorders. The integration of genetic screening, ECG assessment, and molecular diagnostics is crucial for early detection, risk stratification, and therapeutic intervention in LDB3-related diseases. With ongoing advancements in gene therapy and targeted molecular treatments, LDB3 remains a promising focus for future cardiac and neuromuscular disease research.

Conflicts of interest : none

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