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Exploring human bromodomain-containing protein 2 (BRD2) genetic variants in juvenile myoclonic epilepsy (JME): Insights from genetic and gene enrichment analysis

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Abstract

Purpose: Juvenile myoclonic epilepsy (JME) is a common subtype of genetic generalized epilepsy characterized by myoclonic jerks, generalized tonic–clonic seizures, and occasional absence seizures. Although several susceptibility genes have been implicated in JME, the contribution of coding variants within the bromodomain-containing protein 2 (BRD2) gene remain inadequately understood**.** This study investigates genetic variants within exon 13 of the Bromodomain Containing Protein-2 (BRD2) gene in juvenile myoclonic epilepsy (JME) patients.

Methods: A cohort of 55 JME patients and 55 healthy controls was analysed using Sanger sequencing. Mutational changes in the BRD2 gene were identified in 39 JME participants, with sequence data deposited under GenBank accession numbers KX173310 to KX173324. Demographic analysis revealed JME prevalence in adolescents and children. In silico analysis identified single nucleotide polymorphisms (SNPs), while gene enrichment and protein-protein interaction (PPI) networks evaluated BRD2's functional role.

Results: Mutational changes were detected in 39 JME patients, and the corresponding sequences were deposited in GenBank (KX173308 - KX173324). *In silico* analysis revealed recurrent SNPs, including G>A at position 3947, C>T at position 4092, and G>A at position 4107 (relative to reference sequences). Gene enrichment and PPI analysis underscored BRD2's involvement in chromatin remodelling, DNA replication, and transcriptional regulation. Additionally, BRD2 was associated with pathways linked to cancer, highlighting its therapeutic potential.

Significance: The findings highlight the potential contribution of BRD2 exon 13 variants to JME susceptibility and emphasize the importance of BRD2-mediated regulatory pathways in epilepsy pathogenesis. These results provide a foundation for future functional studies and may facilitate the development of targeted therapeutic strategies in JME.

Highlights

- The study uncovers novel genetic variants within exon 13 of the BRD2 gene, shedding light on potential mutation patterns relevant to Juvenile Myoclonic Epilepsy (JME) and its associated clinical manifestations.
- Through demographic and clinical characterization, the study reveals intriguing insights into the prevalence of JME across different age groups and genders, alongside essential physiological markers such as weight, height, and BMI.
- Utilizing gene interactomics and enrichment analysis, the study elucidates BRD2's pivotal role in crucial cellular processes like chromatin remodeling, DNA replication, and transcriptional regulation, underscoring its significance in disease susceptibility and potential therapeutic targeting.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a subsyndrome of genetic generalised epilepsies (GGE) that affects adolescents and adults. It accounts for 5–10% of all epilepsy syndromes in adults and adolescents, and is characterized by arrhythmic, bilateral, single or repeated, irregular myoclonic jerks that occur predominantly after awakening, along with generalized tonic-clonic and absence seizures [1]. Genetic generalised epilepsies are characterised by complex patterns of inheritance [2]. Extensive genetic research has been conducted to elucidate the hereditary nature of JME. Findings indicate that JME is associated with various genetic variations linked to multiple chromosomes [3]. Family-based linkage studies, candidate gene analyses, and next-generation sequencing approaches have identified several genes implicated in JME, including those encoding ion channels, neurotransmitter receptors, and proteins involved in synaptic transmission and neuronal development. Variants in genes such as EFHC1, GABRD, CACNB4, CLCN2, and SCN1A have been associated with altered neuronal excitability and seizure susceptibility. Nevertheless, these genes account for only a proportion of JME cases, indicating that additional genetic determinants remain to be discovered. [4].

An elevated risk of JME is conferred by genes that encode ligand-gated channels. Bromodomain-containing protein 2 (BRD2) has attracted considerable attention because of its biological functions and chromosomal localization. The BRD2 gene, situated on chromosome 6p21.3, lies within the epilepsy susceptibility locus EJM1, which has repeatedly been implicated in JME through linkage and association studies. During embryonic neurodevelopment, cortical organization, and establishment of neural circuits, the transcriptional regulator protein BRD2 and other genes expressing Bromodomain motifs are strongly expressed [5]. Chromosomal region 6p21.3 is associated with JME, according to many association and linkages studies [6]. The genetic variations and single nucleotide polymorphisms (SNPs) in the promotor region, regulatory and no-coding regions, of human BRD2 gene are susceptible to seizure triggering in JME [7]. Information regarding sequence variations within coding regions of the BRD2 gene, particularly those capable of altering protein structure and function, remains limited. Exonic mutations may have profound biological consequences by modifying protein interactions, chromatin-binding capacity, or transcriptional activity [8]. Therefore, characterization of coding variants is essential to elucidate the functional significance of BRD2 in the pathophysiology of JME.

In addition to identifying disease-associated variants, integrating genetic findings with bioinformatic analyses provides deeper insights into disease mechanisms. Protein–protein interaction networks and functional enrichment analyses can reveal the biological pathways in which candidate genes participate, thereby linking genomic alterations with cellular processes. Such approaches facilitate the identification of molecular networks related to chromatin remodelling, DNA replication, transcriptional regulation, and other pathways that may contribute to epileptogenesis and represent potential therapeutic targets.

Therefore, this study aimed to investigate genetic variations and gene enrichment through *in silico* analysis, seeking to elucidate how these specific genetic variations in exon 13 of BRD2 gene in individuals affected by JME. By integrating molecular and computational methodologies, this study seeks to expand current knowledge regarding the genetic basis of JME and provide novel insights into the biological mechanisms underlying seizure susceptibility.

2. Material and Methods

A cohort of fifty-five JME patients who visited epilepsy clinics at Nizam's Institute of Medical Sciences (NIMS), Hyderabad, India, and Girija Neuro Centre, Vijayawada, India, from January 2014 to February 2020, was studied. Prior to their inclusion, all participants, including those under 16 years old, provided written informed consent along with consent from their parents or guardians. The acquisition of data for analysis was authorized by the institutional ethics committee of MNR Medical College and Hospital, Fasalwadi, Sangareddy, Telangana (Ref: MNRMC/EC/638).

2.1. Selection criteria

The selection of JME cases followed the criteria of the Commission on Terminology of the International League Against Epilepsy (ILAE) [9]. JME cases aged between 8–12 years, with myoclonic seizures and Electroencephalogram (EEG) pattern with generalized epileptiform activity were included. Age and gender matched healthy individuals free from any form of epilepsy, and other neurological disorders were considered control subjects (n = 55). Cases with other chronic neurological disorders, including migraine, intellectual disability, status epilepticus, astatic seizures, and other epilepsy syndromes, were excluded.

2.2. Data collection

Self-report questionnaires, validated by seven neurologists and epileptologists, were developed to gather clinicodemographic details. These details encompass the status of education and employment, food habits, types of seizures, timing of seizure expression, frequency and duration of seizures, onset of seizures, EEG findings, and specifics regarding anti-seizure medication.

2.3. DNA isolation and purification

5ml of peripheral venous blood were drawn and kept at 40^0C in an EDTA container. Following the manufacturer's instructions, the DNA was extracted using the NucleoSpin Blood Kit procedure. The standard value of OD260 1.0 = 50µg/ml for double-stranded DNA was used to compute the extracted DNA concentration. Using A260/A280 ratio of 1.8, the purity of the DNA was evaluated (Fig. 1).

After designing the appropriate primers using Primer3 (https://primer3.ut.ee/), exon 13 of the BRD2 gene was amplified using polymerase chain reaction (PCR). Every reaction comprised of 50 µL final volume composed with 10µL Template DNA, 6µL Emerald PCR master mix buffer, 1µL Forward Primer (BRD2-F: 5'- CCT GCC TTC TTG ACT GTC TT -3'), 1µL Reverse Primer (BRD2-F: 3'- AGT AAA TGT CCC TGC ATC CC -5') and 32µL Sterile dH2O. Approximately 40 PCR cycles were conducted, with an initial denaturation for 10 seconds at 94°C, followed by denaturation for 30 seconds at 98°C, annealing for 30 seconds at 62°C, and extension for 1 minute at 72°C. Amplified PCR samples were allotted for automated DNA sequencing at Centre for DNA fingerprinting & Diagnosis (CDFD), Hyderabad by using Applied Bio-systems, Genetic analyser, 3130XL instrument, ensuing Sanger's method [10].

2.4. *In silico* analysis of genetic variants

The comparison between the BRD2 exon 13 sequences of 55 patients and control groups was conducted against the reference sequence identified in the NCBI database Accession NM_001113182.3. Utilizing the ClustalX v2.1 [11] multiple sequence alignment (MSA) was performed on the reference sequence, control samples, and sequences obtained from patients to discern any nucleotide alterations. Subsequently, each modified sequence was integrated into the NCBI-GenBank repository.

2.4.1. Protein-protein interaction (PPI) network analysis

Understanding the intricate mechanisms of genes and proteins is of utmost significance. Within this realm, the STRING database (https://string-db.org/) employed to construct a PPI network [12]. The protein names derived from the prioritized genes were utilized as pivotal elements in initiating the construction of a PPI, encompassing a comprehensive array of genes, proteins, and their interconnected relationships [12]. These seed proteins assumed a crucial role in fostering network connections that involved various human proteins. The development of network acquired into account diverse founts of information, encompassing experimental validation, text mining, databases, co-expression patterns, and interactions within close proximity, all scrutinized at a high confidence threshold of 0.7.

2.4.2. Gene Set Enrichment and Pathway Analysis

The investigation delved into the critical biological processes of the attained targets through the utilization of functional Gene Ontology (GO) enrichment [13]. A functionally organized pathway term network was constructed by amalgamating GO terms and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways. Constraints established for gene list enrichment encompassed the two-sided hypergeometric statistical test enrichment/depletion, the correlation test using the Bonferroni step-down method, a minimum GO level of 3 and a maximum GO level of 8, a Kappa score threshold of 0.4, GO fusion false setting, GO group-true setting, and a significance threshold of $p \leq 0.05$. The ShinyGO, a user-friendly graphical

tool for enrichment analysis, facilitated biological significance embedded within an extensive gene list [14]. This study employed the database, employing a significance level of p = 0.05 [15].

3. Results and discussion

3.1. Demographic and clinical manifestation

The demographic and clinical characteristics of participants diagnosed with JME, revealing intricate patterns across age groups, gender, and physiological parameters. The data provide a comprehensive interpretation of the demographic profile of study participants (Table 1). The cohort distribution reveals a predominance of adolescents (52.72%), followed by children (25.45%) and young adults (21.81%), suggesting that JME is most frequently observed in the adolescent age range. The balanced gender representation 49.10% male and 50.90% female facilitates a gender-neutral baseline for further analysis, ensuring that potential sex-specific disparities in health outcomes can be accurately assessed.

Physiological metrics, including mean weight (35.2 kg), height (138.6 cm), and BMI (19.6 kg/m²), provide a comprehensive profile of the participants' general health. These parameters are pivotal for identifying growth trends and deviations within this age-diverse cohort, offering insights into the physical development trajectories associated with JME (Table 1).

Table 1
Demographic, and clinical characteristics of JME participants.

Characteristic	Group	Frequency (%)
Age group (In years)	8–12	14 (25.45%)
	13–18	29 (52.72%)
	19–24	12 (21.81%)
Gender	Male	27 (49.10%)
	Female	28 (50.90%)
Anthropometric parameters		
Weight (kg)		35.2 ± 4.68
Height (cm)		138.6 ± 7.44
BMI (kg/m²)		19.6 kg/m²

3.2. *In silico* analysis of genetic variant

Figure 2 provides an in-depth analysis of SNPs across various GenBank accessions, identifying several mutations with statistically significant occurrences. The multiple sequence alignment (MSA) reveals specific mutations that recur frequently across the dataset, and their significance is assessed through statistical tests, with p-values indicating the likelihood that these variations. The results were revealed, one of the most statistically significant mutations is the Guanine (G) to Adenine (A) transition at position 3947, observed in approximately 28% of the sequences. This mutation is particularly prevalent in GenBank accessions KX173316, KX173319, and KX173320, with a p-value of 0.01, indicating strong statistical significance. The high frequency and statistical relevance suggest this mutation is not random and may have functional or evolutionary importance. At position 4092, Cytosine (C) to Thymine (T) transition is seen in about 15% of the sequences. This mutation affects several accessions, including KX173308, KX173309, KX173310, KX173311, KX173315, KX173317, and KX173321, with a p-value of 0.02, signifying statistical significance. Given its frequency, this mutation may have implications for gene expression or protein function, especially considering its occurrence in multiple significant sequences. The Guanine (G) to Adenine (A) transition at position 4107 is also noteworthy, appearing in approximately 12% of the sequences, particularly in KX173312, KX173314, and KX173322. This mutation exhibits a p-value of 0.03 statistical significance, although its frequency is lower than the others, its consistent appearance across these sequences implies that it may contribute to functional alterations within the genomic regions of interest.

At position 3870, a Cytosine (C) insertion is identified in about 6% of the sequences, specifically within the GenBank accession KX173316, with a p-value of 0.05, placing it at the threshold of statistical significance. While less frequent, this insertion could potentially impact regulatory regions or cause frameshift mutations. The position 4090 presents an interesting case with two distinct mutations: a Cytosine (C) to Thymine (T) transition in approximately 9% of the sequences (p-value 0.04), and a Guanine (G) to Cytosine (C) transition, seen in about 3% of the sequences (p-value 0.05). The dual occurrence of mutations at this position suggests it may be a mutational hotspot, with potential effects on protein coding or regulatory elements.

In addition to these primary SNPs, the dataset reveals sporadic occurrences of other mutations, including transitions, transversions, deletions, and multiple nucleotide changes across various positions. While these mutations occur less frequently and may not reach statistical significance individually, their presence adds to the genetic variability observed across the dataset. In conclusion, the SNPs identified in this analysis are backed by statistically significant p-values, with key mutations, G to A transition at position 3947 (p = 0.01) and the C to T transition at position 4092 (p = 0.02) standing out for their high frequency and potential biological relevance (Fig. 2). These findings provide valuable insights into the genetic diversity of

these sequences, supporting the need for further functional studies to determine the exact role of these mutations in gene regulation, protein function, and evolutionary adaptation.

Furthermore, performed gene enrichment analysis with BRD2 gene essential for understanding the functional implications of genetic mutations. While variation analysis identifies specific mutations, enrichment analysis provides context by revealing the biological pathways and cellular processes these genes influence. This integration helps to clarify how genetic variations disrupt key functions, such as chromatin remodelling or transcription regulation, which may drive disease progression. It also aids in identifying potential therapeutic targets by highlighting altered pathways, paving the way for more effective, personalized treatments. Ultimately, this approach bridges the gap between genetic findings and their biological and clinical significance, enabling more precise interventions in diseases like cancer and epilepsy.

3.3. Gene interactomics and enrichment analysis

The BRD2 plays a central role in regulating chromatin structure and transcription. As a member of the bromodomain and extra-terminal (BET) family of proteins, BRD2 recognizes acetylated lysines on histones, which are critical markers for gene expression regulation (Table 2 and Fig. 3). This recognition allows BRD2 to other proteins that modulate chromatin states, making it a significant player in processes: cell cycle progression, DNA replication, and transcription. By binding to acetylated histones like H4C6, H4C11, and H4C3, and interacting with bromodomain proteins like BRD3 and BRD4, BRD2 influences chromatin accessibility and, consequently, the transcriptional regulation of various genes [16–18].

Several GO terms highlight BRD2's biological functions and its cellular roles. GO:0006338 (Chromatin Remodelling) and GO:0006325 (Chromatin Organization) show BRD2's involvement in modulating chromatin structure, which is essential for regulating gene expression (Table 2) [17]. These processes control access to DNA by transcription factors and other regulatory proteins, affecting how genes are transcribed. Additionally, GO:0006351 (Transcription, DNA-templated) underscores BRD2's involvement in transcriptional regulation by interacting with transcription factors like E2F1, which controls cell cycle progression. BRD2 also plays a significant role in DNA replication-dependent chromatin assembly (GO:0006335), ensuring that newly synthesized DNA is properly packaged into chromatin during replication, which is vital for maintaining genome stability.

BRD2 is predominantly localized in the nucleus, as indicated by GO terms such as GO:0005634 (Nucleus) and GO:0005654 (Nucleoplasm). Its presence in nuclear regions associated with chromatin (GO:0000785) and nucleosomes (GO:0000786) places it at the center of epigenetic regulation, where it modifies histone marks and influences transcriptional activity (Table 2). By interacting with acetylated histones, BRD2 helps establish epigenetic "memory," ensuring that genes are appropriately activated or repressed in response to various signals. This localization and function within the nucleus underscore BRD2's importance in higher-order chromatin organization, which is critical for regulating gene expression, maintaining genome integrity, and ensuring proper cell function [19].

BRD2 has been linked to several diseases, including NUT midline carcinoma (CL:5336) and cancers (DOID:162). In NUT midline carcinoma, BRD2-related chromosomal rearrangements often involve fusions with oncogenes, leading to abnormal activation of transcriptional programs that drive tumor growth (Table 2). More broadly, BRD2's involvement in cancer pathways highlights its potential role in the dysregulation of genes that control cell proliferation, apoptosis, and DNA repair [26]. Altered expression or mutations in BRD2 can result in the mis regulation of these critical pathways, contributing to cancer development. Due to its influence on transcription and chromatin dynamics, BRD2 has become an important therapeutic target in cancers characterized by chromatin abnormalities [20].

The study of genetic variations in the BRD2 gene has also revealed its role in neurological disorders, particularly in JME [10]. The identified mutations in exon 13 of BRD2 in JME patients, indicating that this gene may be involved in the development of epilepsy. Exon 13 codes for a portion of the BRD2 protein that is likely crucial for its interaction with chromatin and other regulatory proteins. Mutations in this region could disrupt BRD2's normal functions, potentially leading to changes in neuronal gene expression and contributing to the onset of seizures. Additionally, the potential connection between BRD2 genetic variations and photic stimulation in JME patients suggests that specific mutations in this gene may influence the brain's response to environmental triggers like light, further implicating BRD2 in the regulation of neural circuits involved in seizure activity.

Given BRD2's diverse roles in cellular processes and its association with diseases, it has become a promising target for therapeutic interventions. Bromodomain inhibitors (BET inhibitors), which block the interaction between BRD2 and acetylated histones, have shown potential in disrupting transcriptional programs might drive diseases such as cancer. In cancer cells, where BRD2 is often overactive, BET inhibitors can reduce the expression of oncogenes and induce cancer cell death. Similarly, in neurological disorders like JME, targeting BRD2 with specific inhibitors could help modulate the expression of genes involved in neuronal excitability, potentially reducing the occurrence of seizures. Future research should focus on elucidating the specific mechanisms by which BRD2 influences disease pathways and exploring the potential of BRD2-targeted therapies in treating cancers and neurological disorders.

Table 2
BRD2 biological, metabolic and diseases process involved in functional enrichment analysis.

ID	Description	Count in Network	strength	False discovery rate (FDR)	Proteins in network
Biological					
GO:0006338	Chromatin remodeling	9of303	1.73	4.67E-11	H4C6,BRD4,BRD3,H4C11,H4C3,BRD2,BRDT,H4C14,H4C7
GO:0006325	Chromatin organization	10of612	1.47	7.65E-11	H4C6,BRD4,BRD3,NSD3,H4C11,H4C3,BRD2,BRDT,H4C14,H4C7
GO:0034728	Nucleosome organization	7of162	1.89	4.76E-09	H4C6,H4C11,H4C3,BRD2,BRDT,H4C14,H4C7
GO:0006334	Nucleosome assembly	6of124	1.94	9.41E-08	H4C6,H4C11,H4C3,BRD2,H4C14,H4C7
GO:0061644	Protein localization to CENP-A containing chromatin	4of18	2.6	7.49E-07	H4C6,H4C11,H4C3,H4C14
GO:0045653	Negative regulation of megakaryocyte differentiation	4of19	2.58	8.06E-07	H4C6,H4C11,H4C3,H4C14
GO:0006335	DNA replication-dependent chromatin assembly	4of32	2.35	4.37E-06	H4C6,H4C11,H4C3,H4C14
GO:0006336	DNA replication-independent chromatin assembly	4of33	2.34	4.37E-06	H4C6,H4C11,H4C3,H4C14
GO:0032200	Telomere organization	4of129	1.74	0.00047	H4C6,H4C11,H4C3,H4C14
GO:0006352	DNA-templated transcription, initiation	4of131	1.74	0.00048	H4C6,H4C11,H4C3,H4C14
GO:2001255	Positive regulation of histone H3-K36 trimethylation	2of3	3.08	0.0019	BRD4,NSD3
GO:0006351	Transcription, DNA-templated	5of518	1.24	0.0029	H4C6,E2F1,H4C11,H4C3,H4C14
GO:0045596	Negative regulation of cell differentiation	5of685	1.12	0.0098	H4C6,E2F1,H4C11,H4C3,H4C14
GO:0000083	Regulation of transcription involved in G1/S transition of mitotic cell cycle	2of21	2.23	0.0302	BRD4,E2F1
GO:0016070	RNA metabolic process	6of1550	0.84	0.0323	H4C6,E2F1,H4C11,H4C3,BRDT,H4C14
	Molecular	of			
GO:0030527	Structural constituent of chromatin	5of101	1.95	4.51E-06	H4C6,H4C11,H4C3,H4C14,H4C7
GO:0070577	Lysine-acetylated histone binding	4of23	2.49	4.51E-06	BRD4,BRD3,BRD2,BRDT
GO:0046982	Protein heterodimerization activity	5of368	1.39	0.0012	H4C6,H4C11,H4C3,H4C14,H4C7
GO:0046983	Protein dimerization	6of1094	0.99	0.0076	H4C6,E2F1,H4C11,H4C3,H4C14,H4C7

ID	Description	Count in Network	strength	False discovery rate (FDR)	Proteins in network
Biological					
	activity				
Cellular					
GO:0000785	Chromatin	11of1285	1.19	1.95E-10	H4C6,BRD4,BRD3,NSD3,E2F1,H4C11,H4C3,BRD2,BRDT,H4C14,H4C7
GO:0043505	CENP-A containing nucleosome	4of18	2.6	2.61E-07	H4C6,H4C11,H4C3,H4C14
GO:0000228	Nuclear chromosome	6of244	1.64	5.86E-07	H4C6,BRD4,E2F1,H4C11,H4C3,H4C14
GO:0000786	Nucleosome	5of133	1.83	2.04E-06	H4C6,H4C11,H4C3,H4C14,H4C7
GO:0000781	Chromosome, telomeric region	4of143	1.7	0.00016	H4C6,H4C11,H4C3,H4C14
GO:0005634	Nucleus	11of7672	0.41	0.0046	H4C6,BRD4,BRD3,NSD3,E2F1,H4C11,H4C3,BRD2,BRDT,H4C14,H4C7
GO:0005654	Nucleoplasm	8of4169	0.54	0.0458	H4C6,BRD4,NSD3,E2F1,H4C11,H4C3,BRD2,H4C14
STRING Cluster					
CL:5336	NUT midline carcinoma	5of5	3.25	2.15E-11	BRD4,BRD3,NSD3,BRD2,BRDT
CL:4766	Structural constituent of chromatin	4of82	1.94	0.00012	H4C11,H4C3,H4C14,H4C7
CL:4773	DNA replication-dependent chromatin assembly	3of27	2.3	0.0003	H4C11,H4C3,H4C14
CL:4775	CENP-A containing chromatin, and DNA replication-dependent chromatin assembly	2of21	2.23	0.0233	H4C11,H4C3
Pathway					
WP2369	Histone modifications	4of65	2.04	3.48E-05	H4C6,H4C11,H4C3,H4C7
WP5114	Nucleotide excision repair in xeroderma pigmentosum	4of75	1.98	3.48E-05	H4C6,H4C11,H4C3,H4C14
Diseases-gene association					
DOID:0060463	NUT midline carcinoma	5of6	3.17	3.95E-11	BRD4,BRD3,NSD3,BRD2,BRDT
DOID:162	Cancer	6of978	1.04	0.0065	BRD4,BRD3,NSD3,E2F1,BRD2,BRDT
	Tissue expression	of			
BTO:0000580	Blood cancer cell	8of1234	1.06	8.21E-05	H4C6,BRD4,BRD3,E2F1,H4C11,H4C3,BRD2,H4C14
BTO:0001690	B-cell lymphoma cell	4of139	1.71	0.001	H4C6,H4C11,H4C3,H4C14
BTO:0000775	Lymphocyte	5of698	1.11	0.0133	H4C6,H4C11,H4C3,BRD2,H4C14
BTO:0000744	Lymphocytic leukemia cell	4of419	1.23	0.0248	H4C6,BRD3,E2F1,BRD2
BTO:0000753	Lymphoid tissue	6of1600	0.83	0.029	H4C6,NSD3,H4C11,H4C3,BRD2,H4C14
BTO:0001271	Leukemia cell	5of1067	0.92	0.0365	H4C6,BRD4,BRD3,E2F1,BRD2

ID	Description	Count in Network	strength	False discovery rate (FDR)	Proteins in network
Biological					
BTO:0000089	Blood	6of1824	0.77	0.0393	H4C6,NSD3,H4C11,H4C3,BRD2,H4C14
BTO:0001546	Chronic lymphocytic leukemia cell	3of222	1.38	0.0422	H4C6,E2F1,BRD2
Subcellular localization					
GOCC:0000785	Chromatin	7of476	1.42	3.00E-06	H4C6,BRD4,E2F1,H4C11,H4C3,H4C14,H4C7
GOCC:0000786	Nucleosome	5of94	1.98	3.00E-06	H4C6,H4C11,H4C3,H4C14,H4C7
GOCC:0000228	Nuclear chromosome	5of320	1.45	0.00019	H4C6,BRD4,H4C11,H4C3,H4C14
GOCC:0031981	Nuclear lumen	8of1850	0.89	0.00026	H4C6,BRD4,NSD3,E2F1,H4C11,H4C3,BRD2,H4C14
GOCC:0005634	Nucleus	10of4787	0.57	0.0018	H4C6,BRD4,NSD3,E2F1,H4C11,H4C3,BRD2,BRDT,H4C14,H4C7
GOCC:0005654	Nucleoplasm	5of1146	0.89	0.0443	H4C6,BRD4,NSD3,E2F1,BRD2
Protein Domains					
PF17035	Bromodomain extra-terminal - transcription regulation	4of4	3.25	9.97E-09	BRD4,BRD3,BRD2,BRDT
PF17105	C-terminal domain of bromodomain protein 4	2of2	3.25	0.0023	BRD4,BRDT
IPR027353	NET domain	4of4	3.25	2.64E-08	BRD4,BRD3,BRD2,BRDT
IPR038336	NET domain superfamily	4of4	3.25	2.64E-08	BRD4,BRD3,BRD2,BRDT
IPR043508	Brdt, bromodomain, repeat I	4of4	3.25	2.64E-08	BRD4,BRD3,BRD2,BRDT
IPR043509	Brdt, bromodomain, repeat II	4of4	3.25	2.64E-08	BRD4,BRD3,BRD2,BRDT
IPR018359	Bromodomain, conserved site	4of26	2.44	2.05E-06	BRD4,BRD3,BRD2,BRDT
IPR001487	Bromodomain	4of41	2.24	9.25E-06	BRD4,BRD3,BRD2,BRDT
IPR036427	Bromodomain-like superfamily	4of43	2.22	9.49E-06	BRD4,BRD3,BRD2,BRDT
IPR001951	Histone H4	2of2	3.25	0.0015	H4C6,H4C7
IPR031354	Bromodomain protein 4, C-terminal	2of2	3.25	0.0015	BRD4,BRDT
SM00297	Bromo domain	4of43	2.22	7.59E-06	BRD4,BRD3,BRD2,BRDT

3.4. Construction of the BRD2-Centered PPI and functional interactomes network

The PPI analysis is crucial for understanding the molecular mechanisms and functional roles of genes in biological processes. By constructing a PPI network for BRD2, reveal its interactions with other proteins, providing insights into its role in chromatin remodelling, gene expression regulation, and cellular processes such as the cell cycle and oncogenesis (Figs. 3 and 4). The BRD2 PPI network shows strong interactions with its homologs, BRD3 and BRD4, which also contain bromodomains. These proteins bind acetylated lysine residues on histones, thus controlling chromatin dynamics and transcription. BRD4, in particular, is essential for recruiting the positive transcription elongation factor b (P-TEFb) to RNA polymerase II, thereby enabling transcriptional elongation [21].

The interactions among BRD2, BRD3, and BRD4 suggest they share critical roles in regulating transcription, chromatin accessibility, and cell proliferation. Their high connectivity in the PPI network emphasizes their shared function in tumorigenesis, as they are often dysregulated in cancers [22, 23]. Another key interactor is NSD3 (also known as WHSC1L1), a histone methyltransferase that modifies histone H3 at lysine 36, a marker

associated with active transcription. NSD3 forms a complex with BRD2 to regulate genes involved in cell cycle progression and oncogenesis [24]. This interaction highlights the role of chromatin modifications in BRD2-mediated transcriptional control, making it relevant to understanding cancer biology, where both proteins are implicated [25].

Additionally, BRD2 interacts with E2F1, a transcription factor critical for regulating genes during the G1/S phase of the cell cycle. BRD2 modulates E2F1 activity, which underscores its role in cell cycle control and cellular proliferation. Given E2F1's pivotal role in driving cell division, its interaction with BRD2 is particularly important in cancer, where dysregulation of both proteins can lead to uncontrolled growth [26]. Histones, especially histone H4 isoforms, are also major interactors in the BRD2 PPI network. BRD2 binds to acetylated histones, which facilitates chromatin remodelling and gene transcription [27]. The ability of BRD2 to recruit transcriptional machinery to acetylated chromatin regions underscores its role in transcriptional activation and chromatin dynamics [18]. Other significant proteins in the BRD2 PPI network include BRDT, a testis-specific protein involved in spermatogenesis, ATAD2, an ATP-dependent chromatin remodeler, and MYC, a proto-oncogene involved in cell proliferation. While MYC does not directly bind BRD2, its transcriptional activity is influenced by chromatin remodelers such as BRD2, making it highly relevant in cancer biology [28]. Overall, the BRD2 PPI network reveals a web of interactions with proteins involved in chromatin remodelling, transcriptional regulation, and cell cycle control. These interactions help elucidate the role of BRD2 in normal cellular processes and its dysregulation in cancer.

The BRD3 and BRD4 are the closest homologs of BRD2, sharing the conserved bromodomain structure that binds acetylated lysine residues on histone tails. Both BRD3 and BRD4 are essential transcriptional regulators involved in chromatin remodelling and transcriptional elongation [29]. BRD4, in particular, plays a pivotal role in recruiting the positive transcription elongation factor b (P-TEFb) to phosphorylate RNA polymerase II, thereby facilitating transcription elongation [21]. BRD3, although less studied than BRD4, performs similar functions by maintaining chromatin accessibility and regulating gene expression. Their high connectivity in the PPI network with BRD2 reflects their shared biological functions, particularly in gene regulation, cell proliferation, and tumorigenesis [22, 23].

The NSD3, also known as WHSC1L1, is a histone methyltransferase that adds methyl groups to histone H3 at lysine 36 (H3K36), a modification associated with transcriptional activation. NSD3 interacts directly with BRD2, forming a complex that regulates the transcription of genes involved in cell cycle progression and oncogenesis [24, 30]. The functional role of NSD3 in chromatin modification is critical for BRD2-mediated transcriptional regulation, as NSD3 can modify the chromatin landscape, making it more permissive for transcriptional activation. This interaction between NSD3 and BRD2 is particularly relevant in cancer biology, where dysregulation of both proteins has been implicated in tumorigenesis [25].

The E2F1 is a transcription factor that regulates the expression of genes required for the G1/S phase transition during the cell cycle. It controls the transcription of a wide array of genes involved in DNA replication, cell cycle control, and apoptosis. BRD2 has been shown to interact with E2F1, thereby influencing the transcriptional output of E2F1-regulated genes [26]. This interaction highlights BRD2's role in cell cycle regulation and underscores its importance in cellular proliferation. Given E2F1's central role in driving cell division, its association with BRD2 is particularly relevant in the context of cancer, where overexpression or dysregulation of these proteins can lead to uncontrolled cell growth [31].

The Histones (H4C3, H4C6, H4C11, etc.), particularly histone H4, are core components of chromatin and are critical for packaging DNA into nucleosomes. BRD2's ability to bind acetylated histones, particularly acetylated lysine residues on histone H4, underscores its role in modulating chromatin structure and regulating gene expression [27]. The interaction between BRD2 and acetylated histones allows BRD2 to recruit transcriptional machinery to specific regions of chromatin, thereby facilitating gene transcription. The tight association of BRD2 with various histone H4 isoforms in the PPI network indicates its significant involvement in chromatin remodelling processes and transcriptional activation [18].

The BRDT is a testis-specific bromodomain-containing protein that shares structural similarities with BRD2 and is involved in the regulation of chromatin dynamics during spermatogenesis. Although BRDT is primarily expressed in the testes, it shares functional properties with BRD2 in recognizing acetylated histones and influencing transcriptional activity [32, 33]. BRDT's role in chromatin remodelling during germ cell development emphasizes the evolutionary conservation of bromodomain proteins in regulating chromatin accessibility and gene expression. Its close association with BRD2 in the network further highlights the functional redundancy and specialization of bromodomain-containing proteins in different biological contexts [34].

The ATAD2 is an ATP-dependent chromatin remodeler that facilitates the opening of chromatin to allow transcriptional machinery access to DNA. ATAD2 contains a bromodomain that interacts with acetylated histones, similar to BRD2 [35]. It is highly expressed in proliferating cells, particularly in cancer cells, where it promotes the transcription of genes involved in cell proliferation and survival. The interaction between ATAD2 and BRD2 suggests a cooperative role in transcriptional regulation, particularly in the context of cancer, where both proteins are frequently upregulated. ATAD2's high connectivity in the PPI network underscores its involvement in various cellular processes related to chromatin remodelling and transcriptional activation [36].

The MYC is a proto-oncogene that functions as a transcriptional activator for a wide array of genes involved in cell growth, metabolism, and proliferation. Although MYC does not directly bind to BRD2, its transcriptional activity is often influenced by chromatin remodelers such as BRD2 [28]. MYC is a central player in oncogenesis, and its upregulation is a hallmark of many cancers. The interaction between BRD2 and MYC-related pathways is critical for understanding how BRD2 influences gene expression programs that drive cell proliferation and tumorigenesis. MYC's high degree of connectivity in the PPI network reflects its role as a master regulator of cell proliferation [37].

SMARCA4, also known as BRG1, is a key ATPase subunit of the SWI/SNF chromatin-remodelling complex. SMARCA4 facilitates the restructuring of chromatin to allow transcription factors access to DNA [38]. The interaction between SMARCA4 and BRD2 suggests that these proteins cooperate in regulating gene expression by altering chromatin architecture. SMARCA4 is involved in the regulation of a variety of cellular processes, including differentiation and tumor suppression. Its high connectivity in the PPI network with BRD2 highlights its importance in chromatin dynamics and transcriptional regulation [38].

CREBBP, or CBP, is a histone acetyltransferase (HAT) that acetylates histones and transcription factors, facilitating chromatin accessibility and transcriptional activation [39]. BRD2 recognizes these acetylated histones through its bromodomains, promoting the recruitment of transcriptional machinery to acetylated chromatin regions. CREBBP's function in acetylating histones and non-histone proteins places it at a central position in regulating gene expression. Its interaction with BRD2 underscores the critical role of acetylation in transcriptional regulation and epigenetic control. CREBBP is highly connected in the PPI network due to its involvement in multiple transcriptional pathways and cellular processes [39, 40].

MED1 is a key component of the Mediator complex, which bridges transcription factors such as BRD2 with RNA polymerase II, facilitating the initiation of transcription. MED1's interaction with BRD2 highlights its role in assembling the transcriptional machinery necessary for gene expression [41]. As part of the Mediator complex, MED1 plays a central role in transcriptional regulation by integrating signals from multiple transcription factors and chromatin remodelers. MED1's high connectivity in the PPI network reflects its involvement in the regulation of a broad spectrum of genes, making it a critical hub in transcriptional networks [41].

In summary, the PPI network of the BRD2 gene reveals a complex web of interactions involving proteins that regulate chromatin structure, transcriptional activation, and cell cycle progression. Proteins such as BRD3, BRD4, NSD3, E2F1, and histones (H4) are highly connected to BRD2, underscoring their critical roles in transcriptional regulation and epigenetic modification. These interactions are central to understanding BRD2's function in normal cellular processes and its dysregulation in diseases such as cancer. Further exploration of the BRD2 PPI network could provide new insights into therapeutic targets, particularly in the context of cancer and other diseases characterized by aberrant gene expression and chromatin remodelling.

4. Conclusion

The present study revealed, significant association between genetic variations within exon 13 of the BRD2 gene and JME. The identified mutations and polymorphisms in BRD2 gene sequences, especially the recurrent SNPs, underscore the genetic diversity within the studied cohort and highlight potential mutation patterns relevant to JME. Moreover, the analysis of BRD2's functional role in chromatin remodelling, DNA replication, and transcriptional regulation elucidates its critical involvement in fundamental cellular processes, providing insights into its implications in disease susceptibility.

Declarations

Conflict of interest: None of the authors has any conflict of interest.

Source of funding: NIL

Data availability statement

The nucleotide sequencing data reported in this study have been deposited in the NCBI GenBank with the Accession numbers of KX173308, KX173309, KX173310, KX173311, KX173312, KX173313, KX173314, KX173315, KX173316, KX173317, KX173318, KX173319, KX173320, KX173321, KX173322, KX173323, KX173324.

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Author contribution

JK, UVP, MM conceptualized the study. JK, MM, UVP, BS, SAJ, GS conducted the data collection and analysis. JK, MM, UVP, BS, SAJ, GS conducted data interpretation, manuscript writing and final proofing. All authors are approved the final version of the manuscript.

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Figures

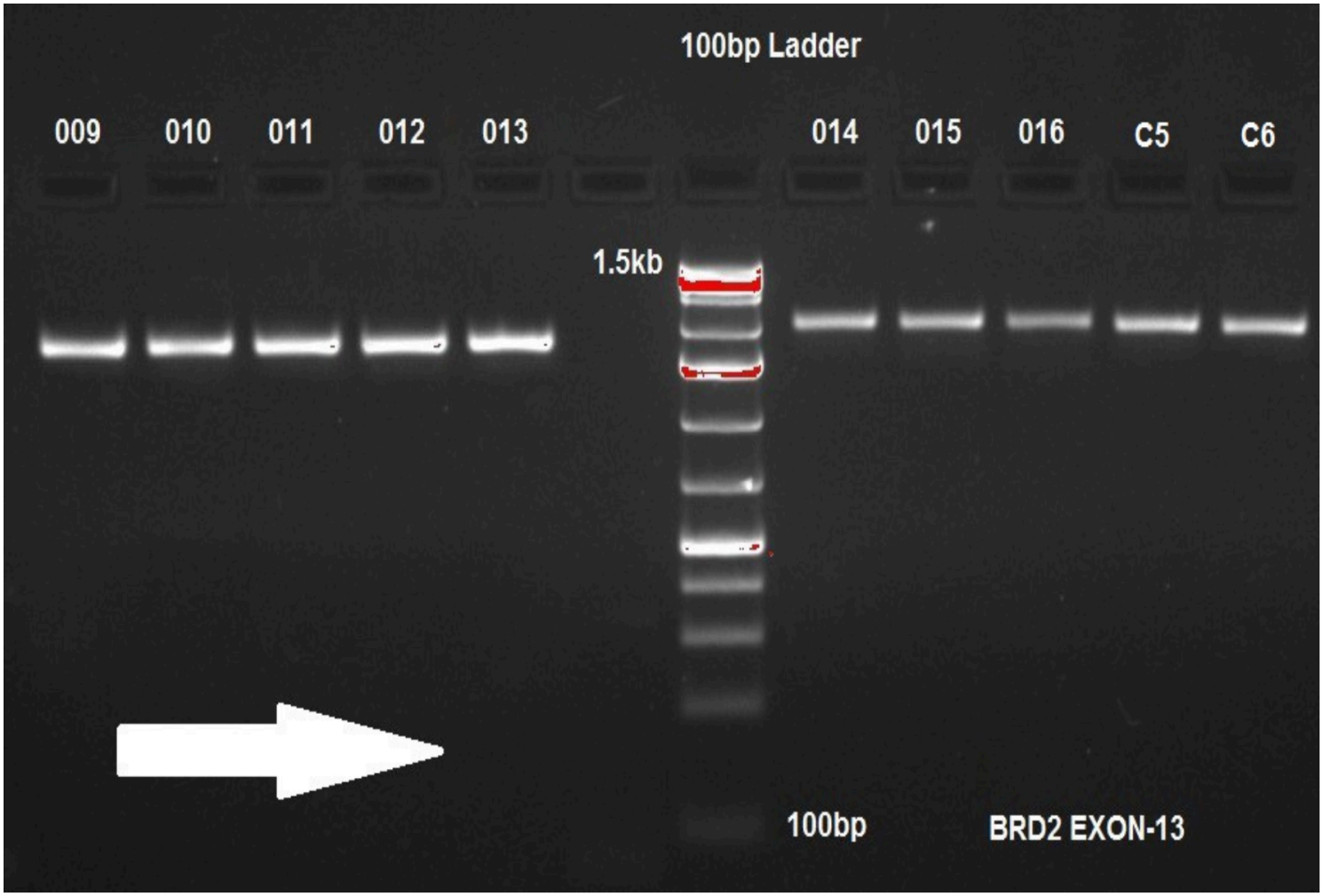


Figure 1

Gel pic showing PCR amplification of exon 13 of BRD2 gene with Forward and reverse primers. Lane C5, C6: Amplified product of exon 13 of controls, Lane 025-036: Amplified products of exon 13 of BRD2 gene in JME Patients.

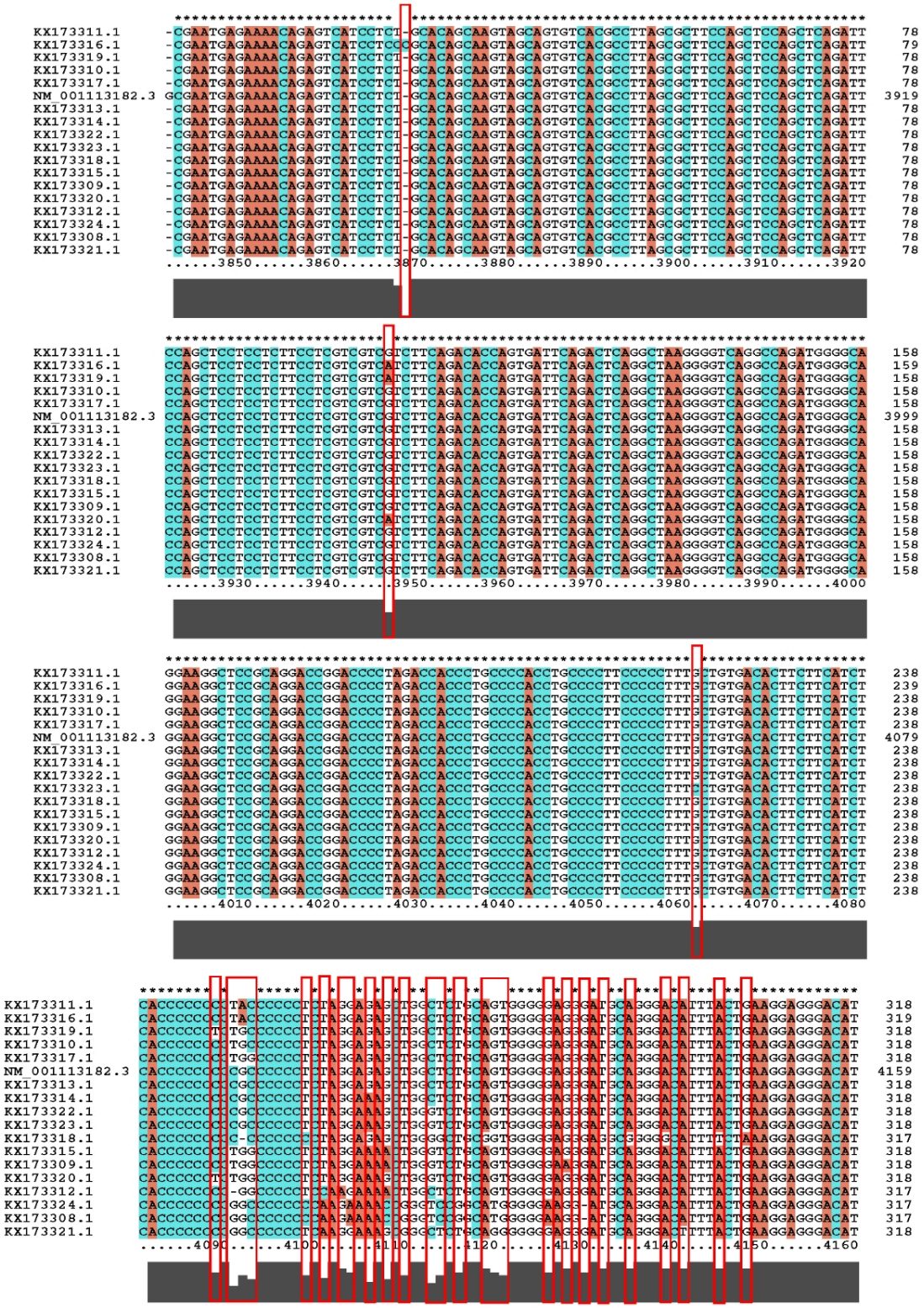


Figure 2

Sequence variation of seventeen JME patient with reference of exon 13 of BRD2 gene.

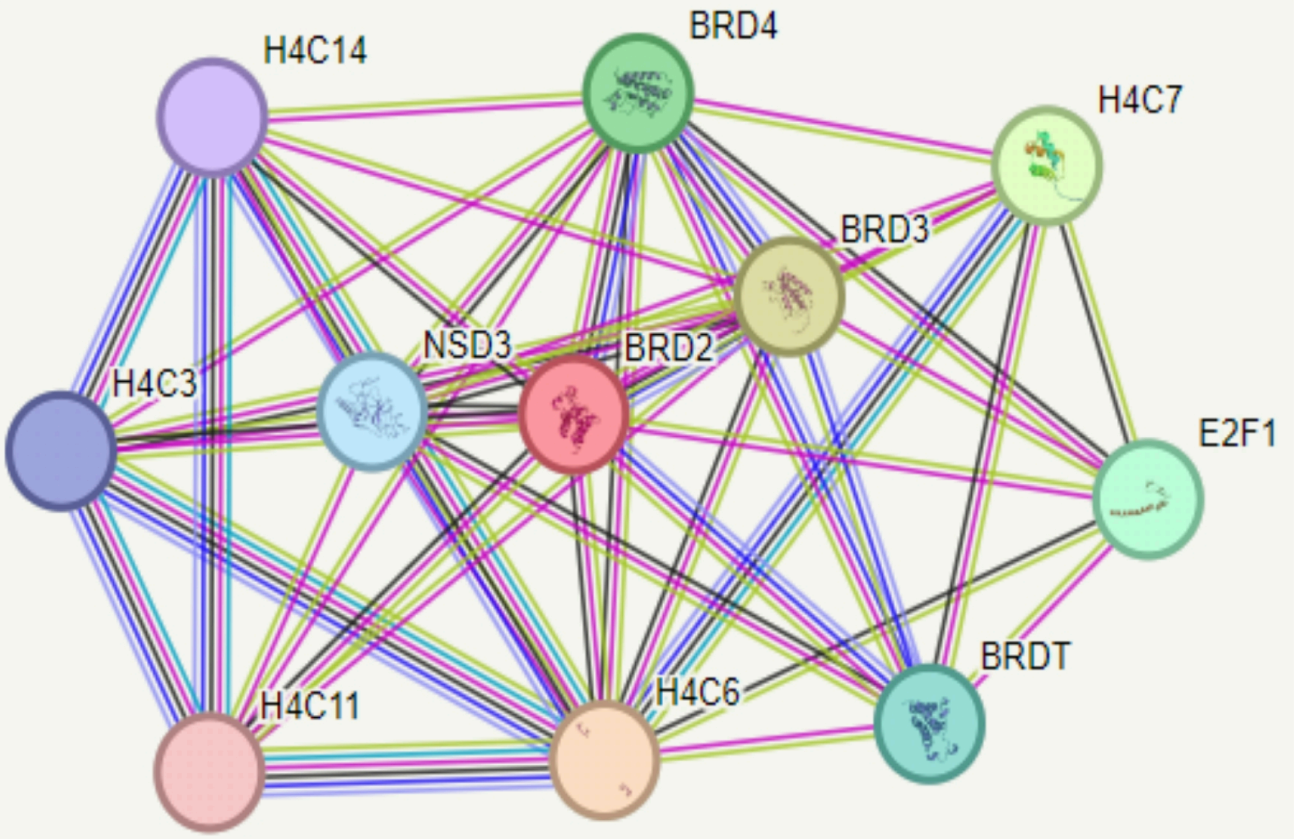


Figure 3

Construction of protein–protein interaction (PPI) network of BRD2 gene.

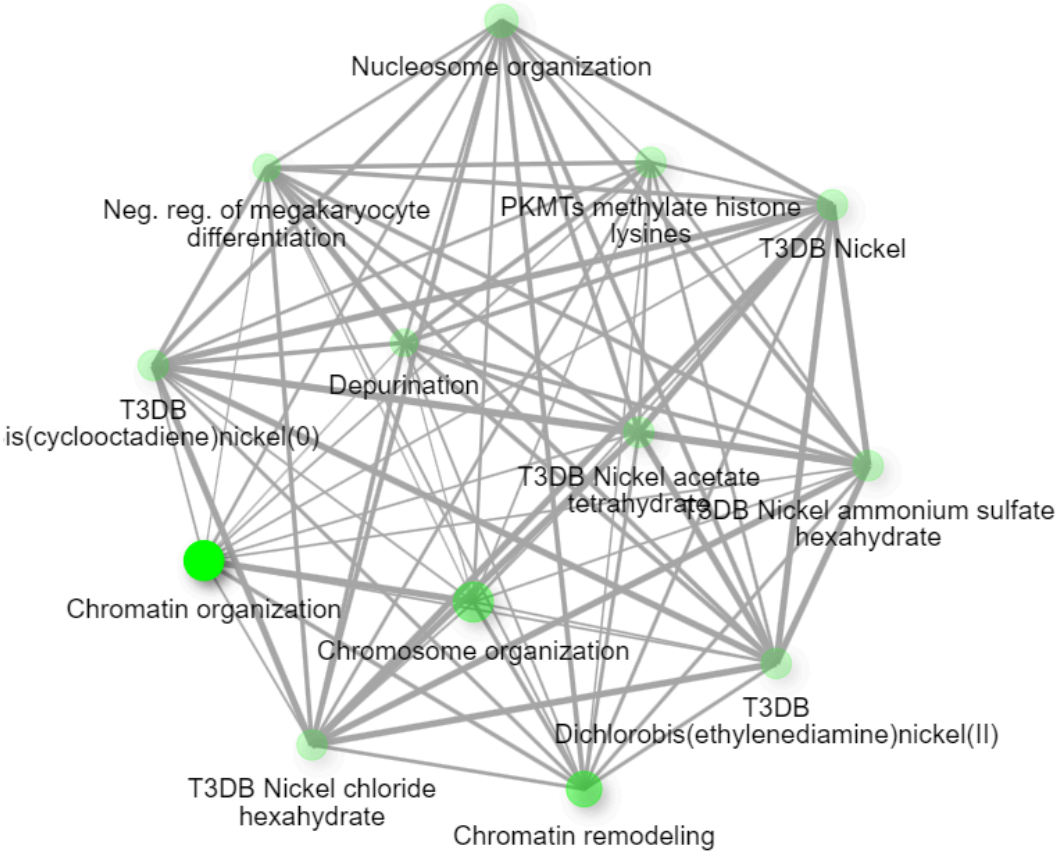


Figure 4

BRD-2 protein functional interactomes

Supplementary Files

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