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Computational Analysis of Cohesin Complex Genes and their Role in the Pathogenesis of AML

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ABSTRACT

Objective: Anomalies in the cohesion complex contribute to the pathogenesis of myeloid malignancies by affecting the self-renewal capacity of hematopoietic and progenitor stem cells, but the underlying mechanisms of this phenotype are not fully understood. Therefore, this study aims to shed light on the relationship between AML pathogenesis and the cohesion complex by comprehensively determining the mutations and expression profiles in the genes constituting the cohesion complex and investigating the effect of expression on survival using bioinformatics databases and tools.

Methods: A total of 96 different mutations were identified in 13 genes. Out of these 96 mutations, 26 were classified as pathogenic/oncogenic. The expression levels of STAG1, REC8, MAU2, CDCA5, and PDS5B were significantly higher in the patient group compared to the healthy group ($p < .01$). Survival analysis based on low and high gene expression profiles revealed that increased REC8 expression was significantly associated with survival ($p < .05$), which is considered a prognostic marker. In STRING analysis, it was determined that hub proteins interact with acetyltransferases ESCO1 and ESCO2 involved in sister chromatid cohesion, with TERF1, a component of the telomere nucleoprotein complex, and with PDS5A and BRCA2, which are functionally related to genetic stability and genetic recombination, respectively.

Results: An increase in language outcomes, particularly in repetition, was observed following the treatments. It was also found that therapy gains were more robust following bihemispheric stimulation of the posterior temporal sites compared to the inferior frontal targets.

Conclusion: Overall, none of the target genes except the mutated REC8 showed a significant and independent effect on the clinical outcome defined as overall survival. However, we have identified the diversity of genetic alterations in individual cohesin subunits through comprehensive molecular analysis. The results may be beneficial in the development of targeted drug therapies and personalized medicine approaches.

Keywords: Cohesion complex, acute myeloid leukemia, leukemogenesis, mutation, gene expression

1. INTRODUCTION

Acute Myeloid Leukemia (AML) is a hematological malignancy with a poor prognosis. It is believed to originate from functionally complementary genetic abnormalities that cause uncontrolled proliferation and halted maturation of myeloid precursor cells (1,2). Despite advancements in cell biology and comprehensive genomic analyses that have revealed possible leukemogenesis mechanisms, the genetic basis of the disease is not yet fully understood. Recent genome-wide sequencing studies have determined frequent recurring somatic mutations in genes encoding members of the cohesin complex (3-7). Cohesin, a multimeric protein complex, is a large ring-like subunit structure involved in regulating chromosome segregation during cell division (3-9). This structure plays an important role in various cellular processes, including chromatid cohesion, repair of damaged DNA, gene transcription, DNA replication, centrosome biogenesis (6,8-11). The ring-like cohesin complex consists of four proteins: structural maintenance of chromosomes (SMC3 and SMC1A), RAD cohesin complex element (RAD21), and cohesin subunit SA (STAG1/STAG2) (6-12). During the cell cycle, cohesin assists different additional subunits, including NIPBL, MAU2, WAPL, PDS5A, PDS5B, and sororin, in the establishment and dissolution of cohesion (12-15). This complex may also interact with transcriptional suppressor CTCF, promoters, enhancers, RNA polymerase II or transcription factors in their initiating and elongating forms to control chromatin structure and gene transcription (13-15). Undoubtedly, cell division is an important process for every tumor cell, including AML blasts, due to the increased proliferative potential of malignant cells. Mutations and expression abnormalities in genes encoding factors of the cohesin complex can contribute to myeloid malignancies by enabling self-renewal of hematopoietic stem and progenitor cells (4,5,7,8,16). We aimed to reveal a comprehensive genetic

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profile of mutations in genes comprising the cohesin complex, including STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5, and understand how these mutations contribute to leukemogenesis by elucidating their functional consequences behind the phenotype.

2. METHODS

2.1. Formation of the study group

The study group was formed by obtaining the AML dataset (n: 872) from the cBioPortal database. The data was accessed through the cBioPortal. The data was downloaded on July 25, 2022.

2.2. Mutation Profile Analysis

The cBio Cancer Genomics Portal (17) is a tool that provides mutation information, copy number alterations, microarray and RNA sequencing-based mRNA expression levels, methylation values, and protein levels from The Cancer Genome Atlas (TCGA) sourced data. The tumor type of interest was selected from the cBio to comprehensively study the mutations determined in the STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 genes in AML patient samples.

2.3. Oncogenic/ pathogenic impact analysis of identified mutations

The oncogenic/pathogenicity of mutations determined in the *STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2,* and *CDCA5* were founded using the scores given by the PolyPhen-2, SIFT, and OncoKB databases.

PolyPhen-2 (18) is an on-line accessible bioinformatics tool that predicts the potential effects of mutations on the stability and function of proteins by using structural and comparative evolutionary analyses of amino acid positions of potential mutations and SNPs. The program predicts the likelihood of a missense mutation damaging the protein based on a combination of these characteristics and provides the user with a score. The SIFT (19) is a tool that estimates whether an amino acid change impacts protein function based on sequence homology and the physical features of amino acids. OncoKB™ (20) is a precision oncology information base developed at the Memorial Sloan Kettering Cancer Center that provides biological and clinical data about genomic alterations in cancer. OncoKB explains the biological and oncogenic impact, as well as the prognostic and predictive significance of somatic molecular alterations.

2.4. Gene expression and survival analysis

GEPIA (21) is a web server that allows users to perform differential expression analysis at the subtype level. GEPIA is used to analyze gene and isoform expression by comparing TCGA and GTEx projects. Therefore, we used this data provider to determine the differential expression of the STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 genes in AML cohort (n: 173) and healthy tissue samples. Survival analyses of genes according to varying m-RNA expression levels were calculated using GEPIA. Overall survival (OS) and disease free survival (DFS) analyses based on Log-rank test with 95% confidence interval were performed to create survival plots.

2.5. Protein-Protein Interaction Analysis

The STRING database (22) is used estimate protein-protein interactions. The purpose of this database is to create a comprehensive and objective global network, including both physical and functional interactions. The predicted interactions of STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 proteins were performed by STRING database, which identifies *physical* and *functional* relationships between proteins.

2.6. Statistical Analysis

The GEPIA database utilizes the differential analysis method to compare gene expression between tumor and healthy control groups. The one-way ANOVA test is used to calculate differential expression. Overall survival analysis was calcuted using Kaplan-Meier curves. The log-rank test was used to compare the low and high expression groups. $p < .05$ was considered statistically significant in all statistical tests.

3. RESULTS

3.1. Demographic and Clinical Features of the Study Cohort

Detailed demographic and clinical characteristics of the dataset consisting of 872 AML patients were presented in Table 1.

3.2. Results of Mutation Profile of Cohesin Complex Genes in AML

In the AML cohort (n=872), it was determined that 15.7% of patients carried mutations in the study genes. The gene with the highest mutation frequency was STAG2 (3%), while no mutations were identified in PDS5A, SMC1B, and CDC5A genes (Figure 1A). A total of 96 various mutations were founded in 13 genes, including 36 missense, 22 nonsense, 15 splice region, and 23 frame shift mutations. Detailed information on the identified mutations is provided in Table 2**.** Additionally, the top 10 genes with the most frequent mutations in the AML cohort were determined as FLT3, DNMT3A, NPM1, IDH2, TET2, RUNX1, NRAS, SRSF2, WT1, and TP53. Based on the presence or absence of mutations in our target genes, we divided the AML cohort into two different groups. When conducting a graph analysis for the top 10 genes, it can be observed that the frequency of FLT3 mutations is similar in both groups. NPM1 mutations are more prevalent in the group with mutations in the target genes (Figure 1B-C). The localization of mutations founded in the domains of proteins belonging to the study genes in AML cohort is demonstrated in Figure 2.

Table 1. *Demographic, clinical and genetic data of patients with AML*

Characteristic	Patient data n:872 (%)
Gender	
Male/Female/NA	311/251/200
Diagnosis age, years	(1-87)
Chromosomal abnormality	
t(8;21)	11 (1.2)
inv(16)	18 (2.0)
11q23	4 (0.4)
t(15,17)	15 (1.7)
Cytogenetic risk	
Favorable	109 (12.5)
Intermediate	116 (13.3)
Unfavorable	132 (15.1)
NA/other	214 (24.5)
Diagnosis type	
FAB subtype	
M0	10 (1.1)
M1	15 (1.7)
M2	13 (1.5)
M3	11(1.3)
M4	35 (4.0)
M5	32 (3.7)
M7	2(0.7)
NA/other	731 (83.8)
Overall Survival Status	
Living	282 (37.0)
Deceased	423 (55.5)
NA	57 (7.5)
Total Mutation Frequency in AML	**Case (Frequency%)**
STAG1 genetic alteration	0.5
STAG2 genetic alteration	5
RAD21 genetic alteration	3
SMC1A genetic alteration	2.5
SMC3 genetic alteration	2.2
PDS5A genetic alteration	0
WAPL genetic alteration	0.3
NIPBL genetic alteration	0.1
REC8 genetic alteration	0.1
PDS5B genetic alteration	1.9
SMC1B genetic alteration	0
MAU2 genetic alteration	0.1
CDC5A genetic alteration	0

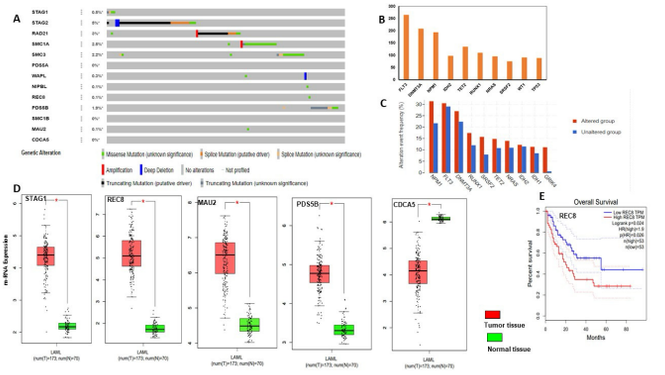

Figure 1. *(A) Distribution of mutations in STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 genes in TCGA AML cohort from cBioPortal. Percentages of overall mutations for each gene are given on the left. (B) Mutation distributions for the first 10 genes in the 872 TCGA AML cohort. (C) Gene Expression Profiling Interactive Analysis (GEPIA) was performed to validate higher expression of seven hub genes (STAG1, REC8, PDS5B, MAU2, and CDCA5) in AML samples compared with normal samples. The red and green boxes represent AML and normal liver tissues respectively. *represented p< .01. (D) Comparison of Kaplan-Meier survival curves of the high and low expression of REC8 in TCGA AML cohort (p< .05). Red line indicates the high expressions of m-RNA; Green line indicates the low expressions of m-RNA.*

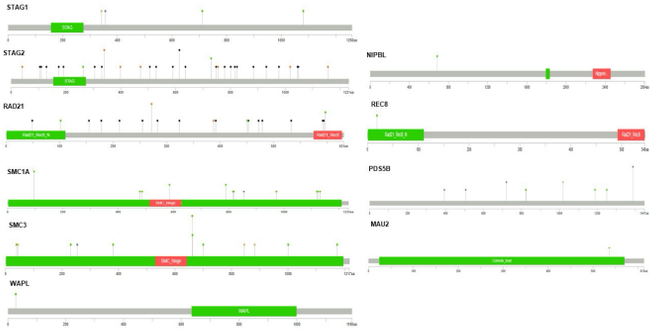

Figure 2. *Schematic representation of domain architecture of the STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 proteins and mutations detected in TCGA AML cohort.*

Table 2. *Characteristics of mutations detected in STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 genes in TCGA AML cohort.*

	Gene	Nt alteration	Rs Number	Alteration Type	Localization	AA position	Type of Cancer and Subtype	Clinical significance		
								Poly-Phen2 (score)	SIFT (score)	OnkoKB (score)
M-1	STAG1	c.3242G>A	NA	Missense mutation	Exon-29	R1081Q	AML	Benign 0.28	Tolerated 0.17	NA
M-2	STAG1	c.2133T>A	NA	Missense mutation	Exon-21	D711E	AML	Benign 0.03	Tolerated 0.68	NA
M-3	STAG1	c.1026+1G>T	NA	Splice region mutation	-	X342_splice	AML	NA	NA	NA
M-4	STAG1	c.1066_1067de	NA	Frame shift deletion	Exon-11	L357Ifs*4	AML-M5	NA	NA	NA
M-5	STAG2	c.123+1G>T	NA	Splice region mutation	-	X41_splice	AML	NA	NA	Likely oncogenic
M-6	STAG2	c.314C>G	NA	Nonsense mutation	Exon-6	S105*	AML	NA	NA	Likely oncogenic
M-7	STAG2	c.328C>T	NA	Nonsense mutation	Exon-6	R110*	AML	NA	NA	Likely oncogenic
M-8	STAG2	c.385_385+1insAA	NA	Frame shift insertion	-	G129Efs*17	AML	NA	NA	Likely oncogenic
M-9	STAG2	c.526dup	NA	Frame shift insertion	Exon-8 STAG domain	C176Lfs*2	AML	NA	NA	Likely oncogenic
M-10	STAG2	c.581_591del	NA	Frame shift deletion	Exon-8 STAG domain	E194Gfs*12	AML	NA	NA	Likely oncogenic
M-11	STAG2	c.913C>T	COSV54354732	Nonsense mutation	Exon-11 SCD domain	R305*	AML-M4	NA	NA	Likely oncogenic
M-12	STAG2	c.992dup	NA	Nonsense mutation	Exon-11 SCD domain	Y331*	AML	NA	NA	Likely oncogenic
M-13	STAG2	c.1018-1_1018del c.1018-1_1018del c.1018-1_1018del	rs205.802.8000	Splice region mutation	Exon-12 SCD domain	X340_splice	AML-M5	NA	NA	Likely oncogenic
M-14	STAG2	c.1197-1G>A	NA	Splice region mutation	-	X399_splice	AML	NA	NA	Likely oncogenic
M-15	STAG2	c.1519dup.1519dup c.1519dup c.1519dup	NA	Frame shift insertion	Exon-16	L507Pfs*2	AML	NA	NA	Likely oncogenic
M-16	STAG2	c.1587_1588dup c.1587_1588dup	NA	Frame shift insertion	Exon-17	R530Ifs*47	AML-M5	NA	NA	Likely oncogenic
M-17	STAG2	c.1768C>T		Nonsense mutation	Exon-19	Q590*	AML	NA	NA	Likely oncogenic
M-18	STAG2	c.1840C>T	COSV54351398	Nonsense mutation	Exon-20	R614*	AML	NA	NA	Likely oncogenic
M-19	STAG2	c.1908C>G c.1908C>G c.1908C>G c.1908C>G c.1908C>G c.1908C>G	NA	Nonsense mutation	Exon-20	Y636*	AML	NA	NA	Likely oncogenic
M-20	STAG2	c.2244_2247dup	NA	Frame shift insertion	Exon-23	E750Nfs*2	AML	NA	NA	Likely oncogenic
M-21	STAG2	c.2336dup	NA	Frame shift insertion	Exon-24	N780Efs*5	AML	NA	NA	Likely oncogenic
M-22	STAG2	c.2450del	NA	Frame shift deletion	Exon-25	P817Lfs*55	AML-M5	NA	NA	Likely oncogenic
M-23	STAG2	c.2470G>T	NA	Nonsense mutation	Exon-25	E824*	AML-M1	NA	NA	Likely oncogenic

M-24	STAG2	c.2653dup	NA	Frame shift insertion	Exon-26 GR domain	I885Nfs*10	AML	NA	NA	Likely oncogenic
M-25	STAG2	c.2793dup	NA	Frame shift insertion	Exon-28 GR domain	Q932Tfs*6	AML	NA	NA	Likely oncogenic
M-26	STAG2	c.2929_2930insTATT	NA	Frame shift insertion	Exon-29 GR domain	G977Vfs*8	AML	NA	NA	Likely oncogenic
M-27	STAG2	c.3054-2A>C	NA	Splice region mutation	Exon-29	X1018_splice	AML	NA	NA	Likely oncogenic
M-28	STAG2	c.3143T>A	NA	Nonsense mutation	Exon-30	L1048*	AML	NA	NA	Likely oncogenic
M-29	STAG2	c.3613C>T	NA	Nonsense mutation	Exon-33	R1242*	AML	NA	NA	Likely oncogenic
M-30	STAG2	c.1840C>T	NA	Nonsense mutation	Exon-20	R614*	AML	NA	NA	Likely oncogenic
M-31	STAG2	c.3133C>T	NA	Nonsense mutation	Exon-30	R1045*	AML	NA	NA	Likely oncogenic
M-32	STAG2	c.2401C>T	NA	Nonsense mutation	Exon-25	Q801*	AML	NA	NA	Likely oncogenic
M-33	STAG2	c.1416+1G>A	NA	Splice region mutation	-	X472_splice	AML	NA	NA	Likely oncogenic
M-34	STAG2	c.2265+2T>C	NA	Splice region mutation	-	X755_splice	AML	NA	NA	Likely oncogenic
M-35	STAG2	c.3467+1G>A	NA	Splice region mutation	-	X1156_splice	AML	NA	NA	Likely oncogenic
M-36	STAG2	c.787A>T	NA	Missense mutation	Exon-9 STAG domain	R263W	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-37	STAG2	c.2188G>T	NA	Missense mutation	Exon-23	V730F	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-38	RAD21	c.1782_1783insT	NA	Frame shift insertion	Exon-14	A595Cfs*10	AML-M4	NA	NA	Likely oncogenic
M-39	RAD21	c.1774C>T	NA	Nonsense mutation	Exon-14	Q592*	AML	NA	NA	Likely oncogenic
M-40	RAD21	c.1599dup	NA	Frame shift insertion	Exon-12	E534Rfs*3	AML	NA	NA	Likely oncogenic
M-41	RAD21	c.1435A>T	NA	Nonsense mutation	Exon-11	K479*	AML	NA	NA	Likely oncogenic
M-42	RAD21	c.1416dup	NA	Frame shift insertion	Exon-11	P473Tfs*5	AML-M2	NA	NA	Likely oncogenic
M-43	RAD21	c.1175_1176del	NA	Frame shift deletion	Exon-10	C392Sfs*10	AML	NA	NA	Likely oncogenic
M-44	RAD21	c.1162-1G>T	NA	Splice region mutation	-	X388_splice	AML	NA	NA	Likely oncogenic
M-45	RAD21	c.972_973insT	NA	Frame shift insertion	Exon-9	I325Yfs*3	AML-M5	NA	NA	Likely oncogenic
M-46	RAD21	c.815-3_815-2del	NA	Splice region mutation	-	X272_splice	AML	NA	NA	Likely oncogenic
M-47	RAD21	c.532G>T	NA	Nonsense mutation	Exon-6	E178*	AML	NA	NA	Likely oncogenic
M-48	RAD21	c.464_471del	NA	Nonsense mutation	Exon-5	L155*	AML	NA	NA	Likely oncogenic
M-49	RAD21	c.764T>A	COSV52058545	Nonsense mutation	Exon-7	L255*	AML	NA	NA	Likely oncogenic
M-50	RAD21	c.849dup	COSV52059956	Frame shift insertion	Exon-8	V284Rfs*2	AML	NA	NA	Likely oncogenic
M-51	RAD21	c.634G>T	COSV52056385	Nonsense mutation	Exon-6	E212*	AML	NA	NA	Likely oncogenic
M-52	RAD21	c.145dup	COSV52063924	Frame shift insertion	Exon-3	V49Gfs*31	AML	NA	NA	Likely oncogenic

M-53	RAD21	c.1359del	NA	Frame shift deletion	Exon-11	E453Dfs*3	AML	NA	NA	Likely oncogenic
M-54	RAD21	c.1790T>A	NA	Missense mutation	Exon-14	F597L	AML	Probably damaging (00.97)	Deleterious (0.00)	NA
M-55	RAD21	c.1352T>G	rs144953114	Missense mutation	Exon-11	L451R	AML	Probably damaging (0.99)	Deleterious (0.00)	NA
M-56	RAD21	c.305A>G	NA	Missense mutation	Exon-4 SMC3 Domain	E102G	AML	Probably damaging (0.99)	Deleterious (0.00)	NA
M-57	SMC1A	c.3367C>T	NA	Missense mutation	Exon-22	R1123W	AML	Possibly damaging (0.79)	Deleterious (0.02)	NA
M-58	SMC1A	c.2918A>G	NA	Missense mutation	Exon-19	Y973C	AML	Possibly damaging (0.85)	Deleterious (0.01)	NA
M-59	SMC1A	c.2369G>A	COSV59127614	Missense mutation	Exon-15 – Coil-coiled Domain	R790Q-	AML-M2/ M5	Probably damaging (1.00)	Deleterious (0.00)	NA
M-60	SMC1A	c.1756C>T	COSV59128824	Missense mutation	Exon-11	R586W	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-61	SMC1A	c.287G>A	COSV59128385	Missense mutation	Exon-2	R96H	AML-M1	Probably damaging (1.00)	Deleterious (0.00)	NA
M-62	SMC1A	c.1757G>A	COSV59127689	Missense mutation	Exon-11	R586Q	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-63	SMC1A	c.2563G>T	COSV59129560	Nonsense mutation	Exon-17	E855*	AML	NA	NA	NA
M-64	SMC1A	c.2447G>A c.2447G>A	COSV59131378	Missense mutation	Exon-16	R816H	AML	Probably damaging (0.99)	Deleterious (0.00)	NA
M-65	SMC1A	c.1460C>G	NA	Missense mutation	Exon-9	A487G	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-66	SMC1A	c.2456T>A	COSV59127812	Missense mutation	Exon-16	I819N	AML	Benign 0.01	Tolerated 0.17	NA
M-67	SMC1A	c.3358A>G	NA	Missense mutation	Exon-22	K1120E K1120E	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-68	SMC1A	c.3391G>A	NA	Missense mutation	Exon-22	G1131R	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-69	SMC1A	c.1435C>A	NA	Missense mutation	Exon-9	Q479K	AML	Benign 0.00	Tolerated 0.92	NA
M-70	SMC3	c.117T>A	NA	Missense mutation	Exon-3	S39R	AML-M5	Probably damaging (1.00)	Deleterious (0.00)	NA
M-71	SMC3	c.130+1G>A	NA	Splice region mutation	-	X44_splice	AML	NA	NA	NA
M-72	SMC3	c.691G>C	NA	Missense mutation	Exon-9	E231Q	AML	Probably damaging (0.94)	Deleterious (0.00)	NA
M-73	SMC3	c.1982G>C	NA	Missense mutation	Exon-19	R661P	AML	Probably damaging (0.97)	Deleterious (0.00)	NA
M-74	SMC3	c.1985G>A	NA	Missense mutation	Exon-19	G662D	AML	Probably damaging (1.00)	Deleterious (0.00)	NA

M-75	SMC3	c.2099T>G	NA	Missense mutation	Exon-19	L700R	AML	Benign 0.01	Tolerated 0.07	NA
M-76	SMC3	c.2535+1G>A	NA	Splice region mutation	-	X845_splice	AML	NA	NA	NA
M-77	SMC3	c.1142G>A	NA	Missense mutation	Exon-13	R381Q	AML	Probably damaging (0.97)	Deleterious (0.02)	NA
M-78	SMC3	c.1982G>C	NA	Missense mutation	Exon-19	R661P	AML	Probably damaging (0.97)	Deleterious (0.00)	NA
M-79	SMC3	c.2644+2T>C	NA	Splice region mutation	-	X882_splice	AML	NA	NA	NA
M-80	SMC3	c.760A>T	NA	Nonsense mutation	Exon-10	R254*	AML	NA	NA	NA
M-81	SMC3	c.3001A>G	NA	Missense mutation	Exon-25	I1001V	AML	Benign 0.02	Tolerated 0.06	NA
M-82	SMC3	c.3521C>T	NA	Missense mutation	Exon-28	T1174I	AML	Probably damaging (0.99)	Deleterious (0.00)	NA
M-83	SMC3	c.1984G>T	NA	Missense mutation	Exon-19	G662C	AML	Probably damaging (0.99)	Deleterious (0.00)	NA
M-84	WAPL	c.81A>C	NA	Missense mutation	Exon-2	K27N	AML	Possibly damaging (0.89)	Deleterious (0.00)	NA
M-85	NIPBL	c.2054A>T	NA	Missense mutation	Exon-10	D685V	AML	Benign 0.02	Tolerated 0.06	NA
M-86	REC8	c.57G>T	NA	Missense mutation	Exon-3	W19C	AML	Probably damaging (0.99)	Deleterious (0.00)	NA
M-87	PDS5B	c.1180A>T	rs750827034	Nonsense mutation	Exon-11	R394*	AML	NA	NA	NA
M-88	PDS5B	VCc.4169del c.4169del	NA	Frame shift deletion	Exon-33	N1390Mfs*4	AML-M5	NA	NA	NA
M-89	PDS5B	c.2170dup	NA	Frame shift insertion	Exon-20	R724Pfs*16	AML	NA	NA	NA
M-90	PDS5B	c.1520dup	NA	Frame shift insertion	Exon-14	D508Gfs*4	AML-M1	NA	NA	NA
M-91	PDS5B	c.2469G>T	NA	Missense mutation	Exon-22	M823I	APL with PML-RARA (AML-M3)	Benign 0.02	Tolerated 0.21	NA
M-92	PDS5B	c.2475+1G>T	NA	Splice region mutation	-	X825_splice	AML	NA	NA	NA
M-93	PDS5B	c.3057-1del	rs868311964	Splice region mutation	-	X1019_splice	AML	NA	NA	NA
M-94	PDS5B	c.3748C>T	rs534821517	Missense mutation	Exon-32	R1250W	AML	Probably damaging (1.00)	Deleterious (0.00)	NA
M-95	PDS5B	c.3562A>G	NA	Missense mutation	Exon-31	T1188A	AML	Benign 0.11	Tolerated 0.49	NA
M-96	MAU2	c.1607C>T	NA na	Missense mutation	Exon-17	S536L	AML	Benign 0.02	Tolerated 0.19	NA

Abbreviations: M: Mutation; NA: Not available; ; Nt: Nucleotid; Rs: Register; ; AA: Amino acid; Inv: Inversion: t: translocation

3.3. Cohesin core subunit genes: STAG1/2, RAD21, SMC1A, SMC1B, SMC3, and REC8

Among the six core genes of the complex, namely STAG1/2, RAD21, SMC1A, SMC1B, SMC3, and REC8, four different mutations (2 missense, 1 frame shift, and 1 splice site mutation) were determined in STAG1. The *STAG1* contains the STAG domain, the stromalin protective region (SCD), and the glutamine-rich (GR) domain (23). The identified p.L357Ifs4 and p.X342_splice mutations are located on the sequence encoding the SCD domain. STAG2, which shares 70% homology with STAG1, has 33 different mutations (2 missense, 11 frame shift, 13 nonsense, and 7 splice site mutations). Among the identified mutations, 23 are putative driver mutations. Deep deletion resulting in homozygous allele loss was observed in 2 patients. The somatic mutation frequency is 4.5%. STAG2 shows homology with STAG1 in terms of domains. Frame shift mutations p.C176Lfs2 and p.E194Gfs12 are located on the STAG domain, while 1 missense alteration (p.R263W), 2 nonsense mutations (p.R305 and p.Y331*), and 1 splice region mutation (p.X340_splice) were identified on the SCD domain. Mutations causing frameshift on the GR domain include p.I885Nfs10, p.Q932Tfs6, and p.G977Vfs8. The mutation p.X755_splice is located on the ubiquitination and acetylation region. Additionally, mutations p.N780Efs5, p.P817Lfs55, p.E824, p.I885Nfs10, p.Q932Tfs6, and p.G977Vfs*8 are found in the Ser/Thr phosphorylation region.

RAD21 gene harbors 19 different mutations (8 frame shift, 6 nonsense, 3 missense, 2 splice region mutations). The somatic mutation frequency is 2.5%. Among the identified mutations, 14 are putative driver mutations. Additionally, there is a gene amplification anomaly in RAD21. RAD21 contains the SMC3 domain (1-103aa), STAG1/2 domain (362-403 aa), SMC1A domain (558-628aa), and the LPE motif (255-257 aa) necessary for the specific cleavage of RAD21 by separase (24). The p.C392Sfs*10 mutation, which causes a change in the reading frame, is located in the STAG1/2 domain. The p.X388_splice mutation, located at the exon-intron boundary of the sequences encoding the STAG1/2 domain, is within the splice site that is 100% conserved across species during evolutionary processes, suggesting that this mutation may cause an anomaly in RAD21 m-RNA expression. The same mutation is within RAD21's NLS signaling region, indicating a potential impact on nucleocytoplasmic transport.

SMC1A gene carries 12 missense mutations and 1 nonsense mutation. The somatic mutation frequency is determined as 2.1%. It contains 2 P-loop NTPase domains and 1 SMC hinge domain (514-629 aa) (25) .The p.R586W/Q missense mutation is located within the SMC hinge domain. The p.Y973C missense mutation is in the phosphorylation region, while p.K1120E is in the acetylation region. Among the 18 AML patients carrying mutations in SMC1A, 7 of them carry at least one FLT3 mutation (frame shift insertion, X583_splice region mutation, and D835Y missense mutation). No mutations were detected in SMC1B in the AML cohort. In SMC3, 14 mutations (10 missense, 3 splice region, 1 nonsense mutation) were identified. The somatic mutation frequency is 1.9%. Missense mutations p.R381Q, p.E231Q, and nonsense mutation p.R254* were identified in the N-terminal coiled coil domain. The p.R254* nonsense mutation has a truncated feature that causes early termination of the polypeptide. Patients carrying this truncated mutation also have oncogenic mutations in FLT3, DNMT3A2, and U2AF2 genes. Furthermore, a missense mutation p.R661P was detected in the SMC hinge domain. Missense mutations p.I1001V and p.T1174I are located in the ATPase domain. Splice region mutations p.X845_splice and p.X882_splice are found in the C-terminal coiled coil domain. In REC8, one missense mutation (p.W19C) was identified. The patient with the REC8 mutation has experienced relapse during treatment and carries a total of 636 different mutations, primarily in IDH2, NPM1, and KRAS genes.

3.4. Cohesin loading genes: NIPBL and MAU2

A missense mutation p.D685V was identified in NIPBL in one patient. In MAU2, we identified a somatic missense mutation p.S536L, which is located in the cohesion load domain. The patient with the MAU2 mutation has relapsed during treatment and also carries FLT3 and WT1 mutations.

3.5. Cohesin dissociation genes: PDS5A, PDS5B, WAPL, and CDCA5

No genetic changes were detected in PDS5A. In PDS5B, 9 different mutations (1 nonsense, 3 frame shift, 2 splice region, and 3 missense mutations) were identified. The somatic mutation frequency is determined as 1.7%. Four mutations (p.R394*, p.N1390Mfs4, p.R724Pfs16, and p.D508Gfs*4) have the potential to cause immature termination of the polypeptide and result in truncated protein. One missense mutation (p.K27N) was identified in WAPL, and it is located in the acetylation region. In WAPL, a deep deletion resulting in homozygous allele loss was found in one patient. No mutations were detected in CDCA5 gene.

3.6. Results of In Silico Analysis of Detected Mutations for Pathogenic/Oncogenic Features

According to the analysis results of the Poly-Phen2, SIFT, and OncoKB tools for predicting pathogenic/oncogenic characteristics, out of the 92 mutations detected in our study, 47 were classified as "*Likely oncogenic*" by OncoKB, and 26 were classified as "*disease-causing*" by the Poly-Phen and SIFT programs. Due to the close-to-1 pathogenic scores and the "affected" features of these mutations according to these two programs, it has been determined that they could have pathogenic properties and have been reported to have disease-causing features. The mutations classified as oncogenic/pathogenic are detailed in Table 2.

3.7. Results of gene expression and survival analysis

Survival analysis and m-RNA expression profiles of key genes were analyzed using the AML cohort (n=173) available on GEPIA, along with matched healthy tissues (n=50) for this cancer type. The gene expression profiles of STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL,

REC8, PDS5B, SMC1B, MAU2, and CDCA5 were examined. The expression levels of STAG1, REC8, MAU2, CDCA5, and PDS5B were determined to be upregulated in the patient group compared to the control group ($p < .01$) (Figure 1-D). Survival analysis based on low and high m-RNA expression profiles revealed that the expression level of REC8 significantly impacted the overall survival (OS) of AML patients. Overexpression of REC8 was shown to contribute to poor prognosis and shortened survival in AML, as depicted in Figure 1E.

3.8. Results of Protein-protein interaction analysis

A protein-protein interaction analysis was completed using the STRING analysis to identfy the functional interactions of STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 proteins in cellular processes. According to this analysis, as observed in Figure 2A, the target genes interact with ESCO1 and ESCO2, two enzymes belonging to a conserved acetyltransferase family involved in sister chromatid cohesion (26). The NDC80 protein, which interacts with SMC1A protein, plays a role in organizing and stabilizing microtubule-kinetochore interactions and is crucial for proper chromosome segregation (27). REC8 is shown to interact with PPP2R1A protein, which is involved in the negative regulate of cell growth and division. STAG1 directly interacts with TERF1, a factor of the telomere nucleoprotein complex (28). PDS5A interacts with BRCA2, which plays a role in maintaining genome stability, particularly in the preservation of the homologous recombination pathway for double-stranded DNA repair (29).

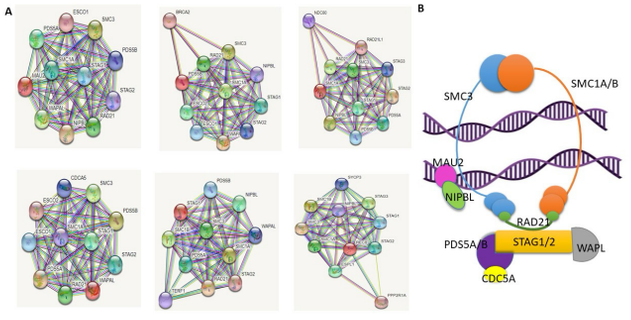

Figure 3. *(A) Schematic representation of known and predicted protein-protein interactions with the STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 genes. Each line has features. [Red line-indicates the presence of fusion evidence; Green line – neighborhood evidence; Blue line – cooccurrence evidence; Purple lineexperimental evidence; Yellow line – textmining evidence; Light blue line—database evidence; Black line—coexpression evidence.]. (B) Depiction of the cohesin complex present in somatic human cells. The core subunits making up the ring-like structure include SMC1A, SMC3, and RAD21. SMC1A and SMC3 both are composed of antiparallel coiled-coil domains joining each other at their hinge domains. RAD21 connects the nucleotide binding domains to close the ring. STAG1/2 joins the complex by associating with RAD21.*

4. DISCUSSION

AML is known to be induced by the collective action of deregulated genes that modify cell proliferation and differentiation. Specifically, chromosomal translocations such as inv(16), t(15;17), t(8:21), t(9;11) are features of AML and play an important role in leukemogenesis. Therefore, approximately 50% of AML cases have a normal karyotype and lack significant chromosomal anomalies (30-32). Recent advancements in next-generation sequencing have allowed us to better understand the genetics of AML and identify numereous mutated genes involved in the pathogenesis of AML. Despite these powerful technological developments, the essence mechanisms underlying leukemogenesis are still not fully elucidated. Therefore, only a few studies have reported that the function of cohesion mutations in the pathogenesis of AML. Increasing evidence suggests that cohesion function deficiency is attributed to cohesion mutations, which may imply a potential tumor suppressor function of cohesion in AML (3-10, 33). In our study, we determined the genetic profiles of genes belonging to the cohesion complex, including STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5, using the genomic and transcriptomic data of 872 patients diagnosed with AML. In addition to our comprehensive mutation profiling, we performed bioinformatics analyses to find the impact of the identified mutations on gene expression profiles and overall survival. Somatic mutations in genes of the cohesion complex are common in different cancer types, including bladder cancer (15-40%), endometrial cancer (19%), glioblastoma (7%), and myeloid leukemias (5-53%) (34). In this study, in parallel with the literature, we identified somatic mutations in the cohesion complex in 15.7% of our AML cohort consisting of 872 patients. Similarly, in a study conducted by TCGA on a cohort of 200 de novo AML patients, one of the most surprising discoveries following whole-genome sequencing was the presence of recurrent somatic mutations in genes encoding the cohesion complex (STAG2, RAD21, SMC3, and SMC1A) in 13% of the patients (31,34). Through genotyping analysis, a total of 96 mutations (36 missense, 22 nonsense, 15 splice region, 23 frameshift mutations) were identified in 13 genes. In our cohort, STAG2 and RAD21 were the most commonly mutated genes in the cohesion complex, while no mutations were found in PDS5A, SMC1B, and CDCA5 genes. The co-occurrence of mutations in SMC1A with WAPL and MAU2 was determined to be statistically significant.

RAD21 is a crucial component of the cohesion complex and forms a trimeric ring with SMC1A and SMC3 (Figure 3B). RAD21 has three binding domains that interact with corresponding proteins: SMC3 (1–103 aa), STAG1/2 (362–403 aa), and SMC1A (558–628 aa); an LPE motif (255-257 aa) (24, 35). Out of the identified mutations in RAD21, 14 are characterized as driver mutations. Driver mutations are known to be the mutations that contribute to the transformation of a normal cell into cancer. In our study group, the L155* mutation located on the LPE binding motif and the Q592* nonsense mutations in the SMC1A protein-binding region have the potential to create a stop codon and result in the formation of

truncated proteins. When we specified the RAD21 mutation analyzes according to AML subtypes, frameshift mutations with oncogenic character were detected in the AML-M2, M4 and M5 subgroups (Table 2). PDS5 plays crucial roles in the establishment, maintenance of sister chromatid cohesion (14,36,37). The regulatory complex of cohesion is regulated positively or negatively with chromosomes depending on which protein binds to the region in PDS5 (14). The missense mutations p.T1188A and p.R1250W found in the study cohort are located in the regulatory region where the NLS signal is present. The p.R394* nonsense mutation in the binding sequence of RAD21 protein in the N-terminal HEAT repeats region has the potential to create a stop codon, leading to truncated protein and loss of the RAD21 protein-binding domain. Mutations in the HEAT repeat regions, namely the 22nd exon/23rd intron boundary region (p.x825_splice) and the 28th exon/29th intron boundary region (p.x1019_splice), can create alternative branch sites in the spliceosome complex, resulting in intron retention, exon skipping, and the generation of non-functional transcripts with intronic extensions. Splice region mutations are one of the main driver mutations in AML and have been reported in different myeloid neoplasms such as MDS, AML, and myeloproliferative neoplasms (MPNs) (38). During the folding stage of the PDS5 protein, multiple HEAT repeats form extended superhelical structures and serve as a scaffold to facilitate the assembly and disassembly of other cohesion complex components (36,37). Mutations in this region can negatively affect the binding and dissociation of other components within the complex. It is known structurally that inositol hexakisphosphate (IP6) binds to the base of the PDS5 clamp (39,40). Other high inositol polyphosphates such as IP5 and IP4, including IP6, are abundant lipid-derived metabolites in eukaryotic cells (39,40). In particular, it is known that IP6 governs protein-protein interactions, thus regulating the interaction between proteins involved in the cohesion complex, such as RAD21 and WAPL, with PDS5 (14,40). In our study, we identified frame shift mutation p.R724Pfs*16 and p.X825_splice mutations in this region, which can have a negative impact on binding. The frameshift mutations p.N1390Mfs*4 and p.D508Gfs*4 have been identified in patients with subtypes M5 and M1, respectively, but the pathogenic properties of these mutations in AML are unknown. In addition, in our study, the benign p.M823I missense mutation was detected in a patient with APL with PML-RARA subtype (AML-M3).I n our study group, it is observed that individuals with high mRNA expression of PDS5A in the AML cohort are statistically significant. PDS5A is known to interact with BRCA2, which plays a role in maintaining genomic stability, particularly in the preservation of the homologous recombination pathway for double-stranded DNA repair. WAPL is an important negative regulator of cohesion and forms a complex with PDS5 to facilitate the release of cohesion from chromatin. There is a binding site for WAPL on PDS5 (40,41). No mutations were detected in these regions in our study. However, the p.K27N missense mutation is located in the acetylation site of WAPL and has the potential to affect the regulation of gene activity. REC8 is the essential protein for the cohesion complex, holding the lateral elements necessary for synaptonemal complex formation and homologous recombination (42). In the AML cohort, there is a p.W19C missense mutation, and it is observed that individuals with high mRNA expression of REC8 in the AML cohort are statistically significant and have shorter overall survival. This finding implies that REC8 expression may serve as a poor prognostic marker.

The SMC1A protein consists of five different domains: two coiled-coil domains, a hinge domain, and N – and C-terminal domains. The N-terminal region contains a nucleotide triphosphate (NTP) binding motif and is responsible for ATP binding (43). The ATP-related domain contains a pathogenic missense mutation p.R96H. This mutation can affect ATP processes such as SMC1A/SMC3 main domain dimerization. In our study group, pathogenic missense and nonsense mutations were identified in the coiled-coil domain, which we present in detail in Table 2. Since SMC proteins form heterodimers, the coiled-coil interactions are reported to be crucial for proper folding of an SMC monomer (43,44). Additionally, it is suggested that the coiled-coil domains may directly interact with DNA and/or be necessary for protein-protein interactions (43-45). Hence, mutations detected in the coiled-coil domain in our study group may impact hinge activity or disrupt interactions with other cohesion subunits. On this domain, the oncogenic p.R790Q missense mutation was detected in patients with AML-M2 and M5 subtypes.

STAG1/2 are subunits of the cohesion complex that are essential for sister chromatid cohesion, chromosome segregation, DNA repair, genome organization, and m-RNA expression (46). Specifically, STAG2 is the cohesion component that harbors the most likely pathogenic mutations. STAG1 protein carries an AT hook to bind telomeric sequences, including a Stromalin Conserved Domain (SCD), in its N-terminal region (46,47). The p.x342_splice mutation may create an alternative branch site in the spliceosome complex, resulting in intron retention, exon skipping, and the generation of non-functional transcripts with intronic extensions. In a patient (AML-M5) carrying the oncogenic/driver mutation NPM1, a frame-shift mutation p.L357Ifs4 was identified in the 11th exon of the STAG1 gene, which can lead to premature termination of the STAG1 polypeptide early in its 34th exon. The *STAG2* is located on the X chromosome and is identified as the most frequently mutated subunit of the cohesion complex. The 11 frame shift mutations identified in the STAG2 gene occur throughout the gene body due to a change in the reading frame and are likely to result in loss of protein expression, possibly due to mRNA decay. Among the identified mutations in the STAG2 gene, 24 are characterized as driver mutations. Specifically, p.X755_splice mutations are located in the acetylation and methylation regions, indicating their oncogenic nature, which may disrupt gene activity. In addition, the p.x340_splice mutation can create an alternative branching site in the spliceosome complex, leading to intron retention, exon skipping and the generation of non-functional transcripts with intronic expansions. This oncogenic mutation was

identified in a patient (AML-M5) carrying the oncogenic/driver mutation NPM1. It has been reported in the literature that alterations in cohesin genes interact with other genetic events in driver genes such as NPM1, potentially promoting malignant transformation (48). The frame shift mutation p.C176Lfs2, which is also oncogenic, is located in the phosphorylation region and can lead to loss of the phosphorylation region, thereby impairing gene activity. The STAG1/2 subunits of the cohesion complex also possess the ability to bind RNA localized in the nucleus (49-51). In cancer cells with STAG2 mutations, STAG inhibition has been reported to cause chromosome segregation defects and homozygous mutations leading to embryonic lethality (50,51). In the STRING protein-protein interaction analysis, our core (hub) proteins interact with two enzymes belonging to a conserved acetyltransferase family involved in sister chromatid cohesion, ESCO1, and ESCO2. Specifically, it has been observed that PDS5A interacts with BRCA2, a protein involved in DNA repair and particularly important for the preservation of homologous recombination pathway in double-stranded DNA repair.

Although we conducted comprehensive molecular profiling analysis of genes responsible for cohesion complex anomalies, we are aware of certain limitations in our study. Current study was conducted with a limited experimental design using bioinformatics tools. Hence, to clarify the impact of STAG1/2, RAD21, SMC1A, SMC3, PDS5A, WAPL, NIPBL, REC8, PDS5B, SMC1B, MAU2, and CDCA5 on the pathogenesis of the complex, further wet lab studies with a larger sample size are required. Understanding the functional consequences of cohesion mutations in a lineage-specific and signal-dependent manner will help identify new pathophysiological mechanisms of the disease and inform the development of new therapeutic targets. These findings indicate that mutations in the cohesion complex may contribute to leukemogenesis.

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Authorship contribution

Research idea: DFA

Design of the study: DFA, DTO

Acquisition of data for the study: DFA

Analysis of data for the study: DFA

Interpretation of data for the study: DFA, DTO, RB

Drafting the manuscript: DFA, DTO, RB

Revising it critically for important intellectual content: DFA, DTO, RB

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