Chromatin Remodellers in Cancer: Unveiling Subunit Dynamics

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Introduction

The SWI/SNF chromatin-remodelling complex is increasingly recognized as a key player in cancer biology, with mutations in its subunits being prevalent across various malignancies. Understanding the impact of SWI/SNF mutations on chromatin structure and gene expression regulation is crucial for identifying potential therapeutic targets. This project focuses on elucidating the role of SWI/SNF mutations in tumour suppression, maintenance and initiation. Through a meta-analysis of subunit composition, gene mutation, and expression patterns in different cancer types, the project aims to uncover commonalities and specificities in SWI/SNF alterations.

Research Question

How did alterations in the SWI/SNF chromatin-remodelling complex's sub-unit composition, gene mutations, and expression influence cancer development and progression?

Methodology

Data Collection

The primary resource for this endeavour was The Cancer Genome Atlas (TCGA), which housed extensive genomic and clinical data from a multitude of cancer patients spanning diverse cancer types. The genomic data encompassed RNA sequencing and gene expression profiles, which were instrumental in determining the subunit composition, gene mutations, and gene expression of SWI/SNF chromatin-remodelling complexes in different cancer types. Additional databases such as Genotype-Tissue Expression (GTEx) and cBioPortal were also utilized to supplement the TCGA data, providing a broader context for normal tissue expression levels and additional genomic alterations, respectively.

Data Analysis

The analysis phase involved scrutinizing the data to identify patterns or trends in the SWI/SNF complex's subunit composition, gene mutations, and gene expression across different cancers. Statistical methods were employed to ascertain the frequency of specific mutations and changes in gene expression. Visualization tools like heatmaps and clustering analysis were utilized to discern patterns or clusters of cancers with similar SWI/SNF profiles.

Results

Cancer	ARID1A	ARID1B	ARID2	SMARCA4	SMARCB1	PBRM1
Bladder - Cancer	20.83	10.56	5.68	90.2	65.96	8.99
Bladder - Normal	23.01	18.07	5.65	49.71	43.88	16.61
Breast - Cancer	32.08	17.09	9.79	79.27	59.38	15.36
Breast - Normal	23.09	17.82	7.34	43.66	43.08	13.38
Cervix - Cancer	22.88	11.67	6.83	84.62	72.79	9.02
Cervix - Normal	24.2	18.09	7.4	50.76	55.64	12.53
Bile Duct - Cancer	13.04	9.16	6.91	82.74	66.51	5.19
Bile Duct - Normal	5.97	3.11	1.38	9.36	15.56	3.29
Colon - Cancer	21.1	13.2	4.92	83.25	68.7	9.55
Colon - Normal	20.81	11.93	5.5	41.2	35.2	10.34
Esophagus - Cancer	41.04	25.68	11.08	72.73	58.76	17.75
Esophagus - Normal	24.19	12.02	6.32	72.6	41.1	10.8
Brain - Cancer	25.35	10.41	5.44	83.18	81.14	9.05
Brain - Normal	12.49	7.69	2.33	71.08	36.62	3.73
Neck - Cancer	23.45	13.23	5.49	71.08	68.25	8.62
Neck - Normal	18.1	12.96	4.24	57.19	43.77	10.75
Kidney - Cancer	12.43	8.73	5.08	69.73	55.91	4.84
Kidney - Normal	17.71	10.58	4.54	51.2	48.59	6.64
Blood - Cancer	91.1	48.57	28.92	68.69	53.06	48.71
Blood - Normal	42.6	14.37	9.37	103.29	45.14	9.92
Liver - Cancer	8.27	3.77	2.18	29.77	29.24	4.04
Liver - Normal	7.77	3.4	1.79	13.42	15.37	3.69
Lungs - Cancer	26.57	11.8	5.06	69.13	53.92	9.93
Lungs - Normal	25.82	15.02	6.81	53.02	38.66	11.42
Ovary - Cancer	32.4	12.1	7.07	63.43	59.05	7.76
Ovary - Normal	27.43	22.3	8.19	44.12	66.03	15.43
Pancreas - Cancer	18.53	12.41	5.35	58.05	55.59	8.16
Pancreas - Normal	8.93	5.45	2.5	16.89	17.35	3.92
Adrenal Gland - Cancer	13.68	10.45	5.13	74.84	51.73	6.02
Adrenal Gland - Normal	12.29	7.43	3.51	50.66	49.85	6.02
Prostate - Cancer	25.21	14.12	6.47	78.61	60.96	10.78
Prostate - Normal	21.17	15.23	7.71	57.52	45.8	10.68
Joint - Cancer	20.71	15.28	5.4	64.8	70.87	11.24
Joint - Normal	8.48	6.7	3.63	44.45	41.92	4.83
Skin - Cancer	24.15	13.45	4.93	87.83	74.5	14.02
Skin - Normal	23.48	20.17	8.87	66.9	46.25	10.71
Stomach - Cancer	29.51	17.57	8.57	47.86	49.04	15.96
Stomach - Normal	17.32	7.31	3.88	27.29	27.41	6.1
Testes - Cancer	29.5	10.77	7.26	128.56	107.08	11.67
Testes - Normal	32.62	8.87	20.83	101.96	95.93	10.71
Thyroid - Cancer	26.49	17.47	6.3	78.08	68.81	10.99

Figure 1: Cancer types with expression level of SWI/SNF subunits (ARID1A/ ARID1B/ ARID2/ SMARCA4/ SMARCB1/ PBRM1)

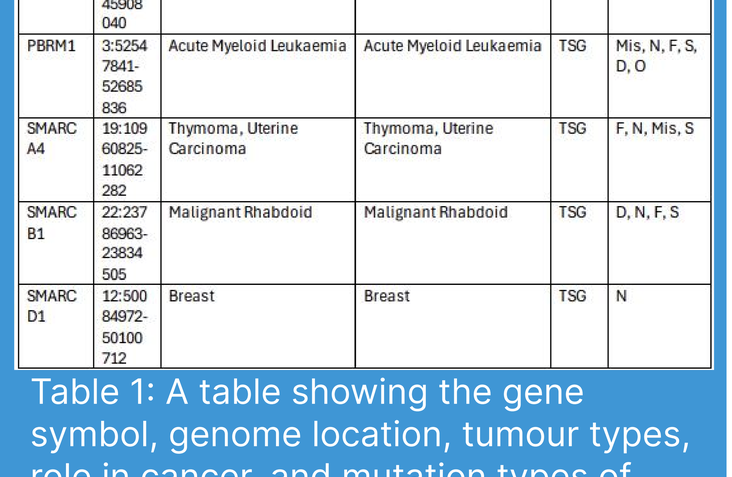
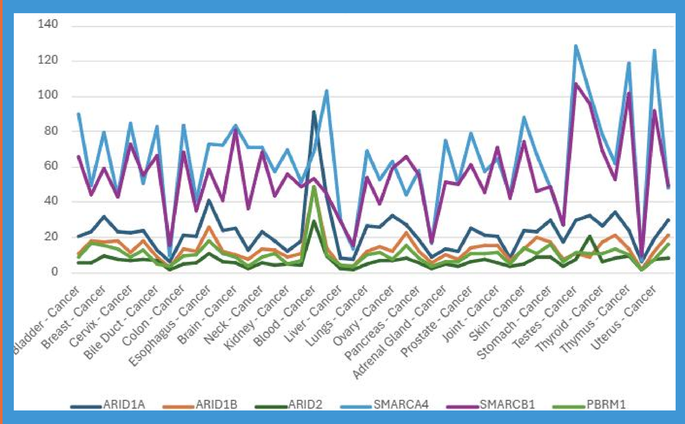


Figure 2: Subunits of SWI/SNF Complexes

Gene Symbol	Genome Location	Tumour Types	Tumour Types	Role in Cancer	Mutation Types
ARID1A	1:26696033-26782110	Clear cell ovarian carcinoma, Breast	Clear cell ovarian carcinoma, Breast	TSG, fusion	Mis, N, F, S, D, T
ARID1B	6:156777374-157210779	Acute Myeloid Leukaemia, clear cell ovarian carcinoma	Acute Myeloid Leukaemia, clear cell ovarian carcinoma	TSG	Mis, F, N, O
ARID2	12:45729665-45908040	Acute Myeloid Leukaemia	Acute Myeloid Leukaemia	TSG	N, S, F
PBRM1	3:52547841-52685836	Acute Myeloid Leukaemia	Acute Myeloid Leukaemia	TSG	Mis, N, F, S, D, O
SMARCA4	19:10960825-11062282	Thymoma, Uterine Carcinoma	Thymoma, Uterine Carcinoma	TSG	F, N, Mis, S
SMARCB1	22:23786963-23834505	Malignant Rhabdoid	Malignant Rhabdoid	TSG	D, N, F, S
SMARCD1	12:50084972-50100712	Breast	Breast	TSG	N

Table 1: A table showing the gene symbol, genome location, tumour types, role in cancer, and mutation types of some SWI/SNF subunits.



Graph 1: Represent the data provided in Figure 1 in an easy to understand way

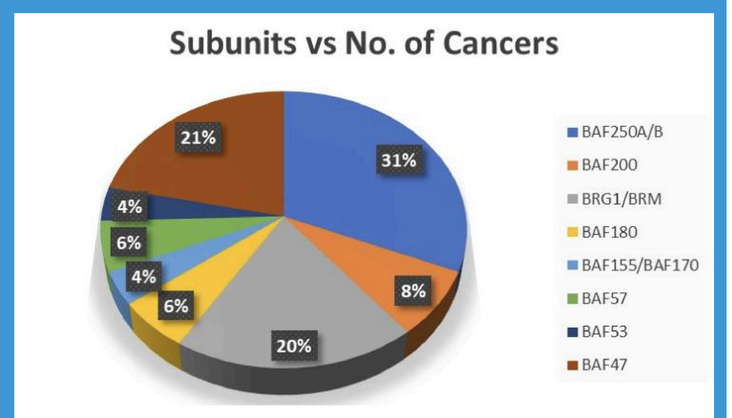


Fig 4.3.1: Involvement Of Swi/Snf Subunits In Cancers, Subunits Vs No. Of Cancer

Future work and Objective

- Expand the scope of the meta-analysis to include more cancer types, more SWI/SNF subunits, and more data sources, to increase the comprehensiveness and generalization of the findings.
- Conduct clinical trials to evaluate the safety and efficacy of the SWI/SNF-based therapies, alone or in combination with other treatments, in patients with SWI/SNF-mutated cancers.

Conclusions

The findings underscored the complexity and heterogeneity of the SWI/SNF complex alterations in cancer. Mutations in key subunits such as ARID1A, SMARCA4, and SMARCB1 were found to be prevalent, suggesting a significant role in tumour suppression and oncogenesis. The project highlighted the potential of these subunits as biomarkers for cancer prognosis and as targets for therapeutic intervention.

Heatmaps generated from gene expression data provided a visual representation of the activity of SWI/SNF-related genes across different cancers, revealing patterns that could be linked to chromatin remodelling and regulatory changes. These insights pave the way for further research into the mechanistic underpinnings of SWI/SNF's role in cancer and underscore the potential for developing targeted therapies that disrupt the aberrant SWI/SNF activity in tumour cells.

Overall, the project represents a step forward in understanding the relationship between chromatin remodelling and cancer, offering a foundation for future studies and the development of novel cancer treatments. The hope is that this research will contribute to a more nuanced understanding of cancer biology and lead to improved outcomes for patients through precision medicine.

References

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