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Article

Inactivation of BAP1 and the Hippo Pathway Defines the Mutational Landscape of Peritoneal Mesothelioma

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Simple Summary

Peritoneal mesothelioma is a rare and aggressive form of cancer of the peritoneum. It is primarily associated with asbestos exposure. This study utilized the AACR project GENIE database to investigate the genomic landscape. The investigation was to identify key somatic mutations in genes and pathways and explore demographic and clinical correlations. In addition, this article aims to discuss potential therapeutic intervention options. Ultimately, this genomic analysis provides a deeper understanding of rare peritoneal mesothelioma and outlines potential biomarkers.

Abstract

Background: Peritoneal mesothelioma is a rare malignancy characterized by limited therapeutic options and poor prognosis. Genomic characterization can enhance the understanding of the molecular mechanisms that lead to this disease, and can contribute to improved survival outcomes through therapeutic targets. Methods: Analysis was performed using a dataset from the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE)® database. Data was analyzed to find statistically significant patterns in the genomic data, histological subtype, and clinical demographics. Results: Through the dataset results we found that the most common somatic mutation was found in the *BAP1* gene (25.98%). Other common mutations were found in the *NF2* (15.19%), *TP53* (9.3%) and *SETD2* (8.3%) genes. Several pathways were found as potential treatment targets. This includes the chromatin remodeling, Hippo, and p53 signaling pathways. Given the size of our dataset, we were unable to draw significant conclusions about certain demographics. Conclusions: This study presents data that can help draw conclusions on common mutations, mutual exclusivity patterns, and demographics at risk for peritoneal mesothelioma. Looking into peritoneal mesothelioma genomic datasets can provide insight which may help develop possible intervention targets for therapeutic treatment.

Keywords: Peritoneal mesothelioma; AACR Project GENIE; somatic mutations; *BAP1*; *NF2*; *TP53*; p53; Hippo signaling pathway; tumor suppressor genes

1. Introduction

Malignant peritoneal mesothelioma (MPM) is a rare cancerous tumor originating from the lining of the peritoneum. Mesothelioma is primarily associated with asbestos exposure, though inherited mutations may contribute to earlier onset in some patients [1]. Pathologically, the disease has been classified into three subtypes: epithelioid, sarcomatoid, and biphasic, each presenting distinct characteristics in terms of appearance, growth, and prognosis [2]. Regarding future care, there are

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several ongoing clinical trials exploring novel treatment approaches for mesothelioma, including immunotherapy, intraperitoneal chemotherapy, targeted therapies, and surgery, as well as combined treatments when appropriate [4–6]. After surgery, the median survival rate ranges from 12-92 months depending on primary treatment, tumor subtype, and patient factors [8,9]. After treatment, patients may experience symptoms such as sleep disturbances, fatigue, pain, sweating, coughing, appetite loss, and lower emotional well-being based on the type of care received [7].

Geographically, mesothelioma cases are most prevalent in Australia and the United States. In 2019, the age-standardized rate (ASR) was 0.43 cases per 100,000 individuals. Australia has been reported to have the highest mesothelioma rate, with an ASR of 0.57 per 100,000 individuals and 700-800 cases per year. South Africa, which has the lowest mesothelioma incidence rate, affects 1 to 2 per one million people a year, resulting in a total of 211 reported cases across African countries [13,14]. Known risk factors for developing this cancer include asbestos exposure, latency period, genetic predisposition, and patient factors [1,15]. Mortality rates vary depending on patient conditions, age, health factors, and tumor subtypes [10–12]. The incidence of the disease has been reported to be higher in males in low-prevalence groups (e.g., industrial groups). A unimodal age distribution is observed for mesothelioma, with most cases occurring in older adults between the ages of 75-84 years [16].

Initial evaluation for suspected mesothelioma typically includes chest X-rays and CT scans to examine mesothelial linings in the walls of serosal cavities, along with open biopsy for potential surgical diagnosis and treatment planning [17]. Since mesothelioma can spread diffusely through different surfaces, surgical approaches may not be a practical option for certain patients. Instead, diagnosis and treatment planning rely on laboratory tests, positron emission tomography scans, and radiographic imaging. Disease stage, metastasis, and careful treatment processes based on patient medical history and conditions are considered when making definitive diagnoses and treatment plans [1,17,18]. To classify the tumor, staging systems categorize tumors based on location and subtype. Pleural mesothelioma is classified by its official staging system known as TNM (tumor size, nodal involvement, and metastasis), while peritoneal and testicular mesothelioma have not established an official staging system. Recent research has found that new investigational therapies, such as targeted therapies, tumor-treating fields, and gene and cell therapies, have been through clinical testing for potential treatments in the future [17,19,20]. Further analysis on mesothelioma pathogenesis is vital for new treatments and diagnoses to help improve emerging treatment strategies to help support the quality of patient and tumor outcomes.

Despite soluble mesothelin-related proteins (SMRP) being a notable diagnostic marker, current studies emphasize possible mutations in the genes *BAP1*, *CDKN2A*, and *NF2* affecting tumor suppression and genetic profiling risks [21–23]. Variants in genes can cause differences in biological and therapeutic outcomes, affecting tumor or treatment response for patients [24,25]. The disease is diagnosed in later stages with a survival rate of 12-92 months based on patient conditions and tumor size. One of the established staging systems, pleural mesothelioma, is divided into four staging phases, with Stage 1 reported to have 9% of cases present, Stage II 14%, and the most notable stages, III and IV, at 65%. Statistics reveal that tumor detection in earlier stages is more difficult compared to later stages, resulting in a lower survival rate [26]. The current gaps in the understanding of the molecular and genetic basis of mesothelioma prolong the timeline for diagnosis and treatment. There arises the need for further research to be conducted on molecules and tumor genes for proper diagnosis and treatment of patients.

The objective of this paper is to recognize genetic factors in mesothelioma in terms of tumor spread, non-responsive treatment, and tumor regression malignancy, which is crucial in progressing new diagnostic methods and therapeutic treatments. Despite current improvements, a thorough understanding of genetic modifications underlying mesothelioma pathogenesis is still in progress and incomplete. This study report is publicly accessible to present a significant mapping of the genetic makeup of mesothelioma and to educate and understand future advancements of new treatments and diagnostic strategies.

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2. Materials and Methods

Ethical approval by the institutional review board was waived by Creighton University Institutional Review Board (Phoenix, AZ, USA) because the data used was from the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE)® database and is therefore already publicly accessible and does not reveal patient information. The cBioPortal (v17.0-public) online software accessed the cohort data on February 6, 2025, including genomic and clinical data entered from 2017 to present.

The AACR GENIE® database utilizes a variety of data from 19 international cancer centers, including whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted gene panels covering 50-555 genes. These different sequencing methods yielded different levels of coverage. Eighty percent of samples were subjected to targeted panel sequencing, which yielded the greatest coverage of over 500×. Fifteen percent of samples were subjected to WES, yielding 150× coverage. The remaining 5% of samples experienced WGS, resulting in approximately 30× coverage. Thirty-five percent of the cohort were matched tumor-normal pairs, which are essential for filtering germline variants. The remaining 65% were composed of tumor-only sequencing specimens.

Each participating institution utilizes individual programs to identify and label mutations, but all methods fall under GENIE harmonization protocols via the Genome NEXUS. For example, GATK is often used for variant detection and ANNOVAR is then used for annotation. However, each institution may have a different version of this software. In addition, variations can exist within individual institutions, as some data come from comprehensive sequencing methods such as WGS or WES, while other data comes from target panels looking at up to 555 specific genes. Patient responses to treatment and their clinical outcomes are often included in the database, however, this information is not available for peritoneal mesothelioma, as these details were not recorded.

Of the large group of head and neck tumor cases, patients with a pathologic diagnosis of peritoneal mesothelioma were identified and sorted as primary (obtained from the site where the cancer began to grow) or metastatic (of a secondary site that spread from the primary tumor). A chi-squared test was then performed on the groups using the proportion of mutated samples in each to compare their rate of mutation frequencies.

Genomic data (e.g., somatic mutations), histological subtype, and clinical demographics (e.g., age, race, and sex) formed the dataset. Cancer-associated genes essential to the study, such as *KMT2D*, *TP53*, and *PIK3CA*, were included in the majority of panel designs, despite slight differences between institutions. Also consistent across panels was the absence of non-actionable genes and the exclusion of structural variants in the analysis. Greater understanding of genetic drivers or tumor progression, resistance, and metastasis is necessary, as comprehensive knowledge of the genetic alterations comprising MPM pathogenesis is still incomplete. This study is designed to use publicly available data to characterize the somatic genomic landscape of MPM, ultimately aiming to adequately inform work on future therapeutics and screening methodologies.

We focused on homozygous deletions and amplifications to evaluate copy number alterations (CNAs) based on the frequency of repeat events. We calculated tumor mutational burden (TMD) through somatic mutations (synonymous and nonsynonymous) per megabase sequenced. Differences in TMB panel size were accounted for with panel size (e.g., total mutations/1.5 for a 1.5 Mb panel). From there, we used linear regression models designed by the AACR Project GENIE consortium to equate TMB values to WES values for comparison. The models are available via GENIE [15], and they account for features including panel size to increase comparability between sequencing platforms in spite of differences in panel size.

Samples with incomplete data were excluded from the analysis. Analysis was done with R/R Studio (R Foundation for Statistical Computing, Boston, MA, USA), and samples with $p<0.05$ were considered statistically significant. Relationships between categorical variables were analyzed using a chi-squared test, and presented as the resulting frequencies and percentages. With continuous variables, normality was examined to divide samples into two groups. Then, a two sided Student's T-test (for normal distribution) or a Mann-Whitney U test (non-normal distribution) was used to

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present results as a mean ± standard deviations (SD). To control the false discovery rate (FDR), we used a Benjamini-Hochberg correction, which accounted for multiple comparisons.

Somatic mutations were filtered to only include nonsynonymous variants - including missense, nonsense, frameshift, and splice site mutations - with a variant allele frequency (VAF) of at least 5% and coverage of at least 100×. Mutations with no or unclear impact on protein function were excluded. GENIE harmonized mutation annotation format files provided all mutation calls, which provides standardized and consistent formatting for reporting abbreviated gene and protein alteration across the different institutions.

3. Results

3.1. Patient Demographics of Peritoneal Mesothelioma

To analyze general demographic trends, primary and metastatic tumor samples were combined due to the limited sample size. Demographic characteristics for 204 tumor samples from 192 patients are summarized in Table 1. In terms of sex, 80 (41.7%) samples were from male patients and 104 (54.2%) from female patients. There are no demographic data for age for this cohort. Regarding ethnicity, 151 patients (78.6%) were classified as non-Spanish/non-Hispanic, 10 (5.2%) as Spanish/Hispanic, and 25 (13.5%) patients had unknown ethnicity. With regard to race, most patients were White (139; 72.4%), followed by Asian (12; 6.3%), Black (8; 4.2%), and Other (10; 5.2%). Race information was unknown for 21 (10.9%) patients. Of the tumor samples, 146 (71.6%) were from primary tumors, while 25 (12.3%) samples were from metastatic tumors, and 10 (4.9%) lacked information regarding tumor origin.

Table 1. Patient demographics for peritoneal mesothelioma.

Demographics	Category	N (%)
Sex	Male	80 (41.7)
	Female	104 (54.2)
Ethnicity	Non-Hispanic	151 (78.6)
	Unknown/Not Collected	25 (13.5)
	Hispanic	10 (5.2)
Race	White	139 (72.4)
	Asian	12 (6.3)
	Black	8 (4.2)
	Other	10 (5.12)
	Unknown	21 (10.9)
Sample Type	Primary	146 (71.6)
	Metastasis	25 (12.3)
	Not Collected	10 (4.9)

3.2. Most Prevalent Somatic Mutations and Copy Number Alterations

The most common mutations found, as shown in Figure 1, were *BAP1* (n = 53; 25.98%), *NF2* (n = 31; 15.19%), *TP53* (n = 19; 9.3%), *SETD2* (n = 17; 8.3%), *TRAF7* (n = 13; 6.4%), *LATS1* (n = 6; 2.9%), *CREBBP* (n = 9; 4.4%), *LATS2* (n = 8; 3.9%), *PBRM1* (n=8; 3.9%), *KMT2D* (n=7; 2.9%). *TERT* and *SF3B1* also showed significant mutation frequencies, and of this list of genes, the most commonly mutated was *BAP1*. Copy number alterations (CNAs) were also examined. Through this, we found loss of heterozygosity (LOH) events were quite prevalent on suppressor genes such as *BAP1* (n = 20, 9.8%), *CDKN2A* (n = 18, 8.8%), and *CDKN2B* (n = 17, 8.3%). In addition, amplifications also showed prevalence, although significantly less than LOH events. These events impact genes such as *WT1* (n = 4, 1.96%) and *MCL1* (n = 4, 1.96%). Figure 1 demonstrates recurrent mutations in MPM after running the OncoPrint program.

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3.3. Genetic Variations by Race and Sex

When grouping cohort data by sex, there were only three genes for which differences were statistically significant. Women had the majority of the enrichment of mutations in the *SETD2* (n = 20 vs n = 4; p = 0.0036) gene and mutations in the *CDC42* (n = 6; p = 0.032) gene occurred strictly in women. However, mutations in the *SLC45A3* (n = 1; p = 0.027) were identified only in male patients. In this cohort, there are no statistically significant differences in mutation enrichment by race. Table 2 contains the corresponding diagnosis rate and p-value in regard to sex for common genetic mutations associated with mesothelioma.

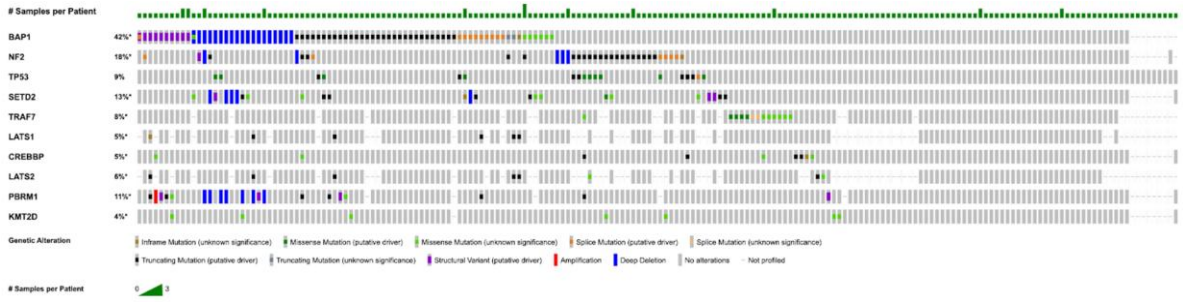

Figure 1. OncoPrint of recurrent mutations in MPM. Star (*) indicates that not all samples were profiled.

Table 2. Sex and associated mutations in patients diagnosed with mesothelioma.

Gene (Chi-Squared)	Male, N (%)	Female, N (%)	P value
SETD2	4 (4.76)	20 (19.42)	$p = 0.0036$
CDC42	0 (0.0)	6 (10.34)	$p = 0.032$
SLC45A3	1 (33.33)	0 (0.0)	$p = 0.027$

3.4. Mutation Co-Occurrence and Mutual Exclusivity Relationships

The most significant co-occurrence patterns were observed between *BAP1* and *PBRM1* (n = 19; p < 0.001) and *LATS1* and *LATS2* (n = 5; p < 0.001). Other significant co-occurrence patterns were observed between *BAP1* and *LATS1* (n = 6; p = 0.013) and *SETD2* (n = 17; p = 0.003). *LATS1* was also identified with significant co-occurrence patterns with *PBRM1* (n = 3; p = 0.035). Furthermore, *PBRM1* also had significant co-occurrence with *KMT2D* (n = 2; p = 0.014). Only one significant mutual exclusivity pattern was identified between *BAP1* and *TRAF7* (n = 0, p < 0.001).

3.5. Primary and Metastatic Mutations

When comparing primary tumors to metastatic, of the significant results, the majority showed mutations found on genes only in metastatic tumors. This group includes mutations found in *CHEK2* (n = 2; p = 0.0187), *SRSF2* (n = 2; p = 0.0188), *PPP2R1A* (n = 2, p = 0.199), and *CARM1* (n = 2, p = 0.0303). There was one instance of a mutation being found on a gene only in primary tumor samples, which was in the *TPM1* (n = 2, p = 0.0230). In the *PBRM1* (n = 6 vs. n = 12; p = 0.0262), there were more instances of mutation in patients with primary tumors, however due to the difference in group sizes, a much greater percentage of metastatic tumors displayed a mutation on this gene. There were no genes with similar numbers of mutation enrichment.

4. Discussion

4.1. Study Overview and Key Findings

This study analyzed data on peritoneal mesothelioma through the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database. Analysis of this data revealed recurrent mutations in key tumor-suppressor genes. Among

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the tumor-suppressor genes analyzed, BAP1, NF2, and TP53 had the most frequent mutations. Regarding sex specific differences in mutated genes, women had significant enrichment in the SETD2 gene. Mutations in CDC42 only occurred in female patients. Mutations in the SLC45A3 gene were only observed in male patients. Based on co-occurrence analysis, BAP1 and PBRM1 is a notable pattern pairing and CHEK2 and SRSF2 when comparing primary and metastatic samples. In this observed dataset, there were no race-specific differences in mutation enrichment.

4.2. Demographic Differences and Mutation Patterns

The observed cohort consisted of 41.7% (n=80) male and 54.2% (n=104) female patients. Notably, female patients had enrichment in the *SETD2* gene (female: n=20, male: n=4, p=0.0036). In addition, mutation in the *CDC42* gene was only observed in female patients (female: n=6, male n=0, p=0.032). Mutation in the *CDC42* gene found exclusively in women suggests that there is a possible sex-linked biological impact that requires further investigation. The *SLC45A3* mutation was exclusive to males (male: 1, female: 0, p=0.027), although only one case was observed.

Ethnically, this cohort was predominantly non-Spanish/non-Hispanic (n=151, 78.6%). In addition, a majority of the patients in the cohort identified White (n=139, 72.4%). This is consistent with studies that suggest there is a higher incidence of peritoneal mesothelioma in non-Hispanic White patients [1]. According to literature, in the United States approximately 90% of new peritoneal mesothelioma cases are diagnosed in non-Hispanic white patients [66]. Understanding that peritoneal mesothelioma has a higher incidence rate among non-Hispanic white patients can provide insight into potential contributing factors to the cancer. Although, in this observed dataset, there were no race-specific statistically significant differences in mutation enrichment. Given the relatively low number of non-White patients in this dataset (Asian: n=12, Black: n=8, Other: n=10, unknown: n=21), a larger more representative cohort is needed to draw significant conclusions about race-specific differences in mutations.

4.3. Commonly-Mutated Genes and Altered Pathways

Consistent with previous literature, our peritoneal mesothelioma cohort exhibited significant mutation within the *BAP1* gene (25.98%) [1,27,28]. This study also identified common somatic mutations in *NF2* (15.19%), *TP53* (9.3%) and *SETD2* (8.3%). Mutations were also observed in the *TRAF7* (6.4%), *LATS1* (2.9%), *CREBBP* (4.4%), *LATS2* (3.9%), *PBRM1* (3.9%), *KMT2D* (2.9%) genes, but to a lesser extent. These findings align with prior studies that have determined that the loss or mutation of the *BAP1* gene is linked to peritoneal mesothelioma [1,27–29]. *BAP1* is associated with tumor-suppressor genes and is related to DNA damage repair pathways [27,28,30]. Another common altered pathway, *NF2*, is associated with the Hippo pathway which is a key component in the regulation of cell proliferation [27,28,31].

Through examination of CNAs, LOH events were predominant in *BAP1* (9.8%), *CDKN2A* (8.8%), *CDKN2B* (8.3%) and less predominant in *WT1* (1.96%) and *MCL1* (1.96%). Along with common mutations within *BAP1*, *NF2*, *TP53*, mutation of the *CDKN2A/B* gene is frequently associated with peritoneal mesothelioma [27,30].

The clinical standard for treatment of peritoneal mesothelioma can be attributed to their interaction with these commonly mutated pathways associated with the mutation of *BAP1*, *NF2*, *TP53*, and *CDKN2A/B* genes. Results from our study and previous literature suggest that peritoneal mesothelioma tumorigenesis is driven by the deactivation of tumor-suppressor genes rather than the activation of oncogenes [1,27–32].

4.4. BAP1 and Chromatin Remodeling

The most frequently mutated gene found in our cohort was *BAP1* (n=53, 25.98%). This is consistent with previous studies, one which found a very similar 23% *BAP1* mutation among their cohort [33]. Other studies have found that *BAP1* loss is often a common defining genomic feature in

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mesotheliomas [33]. *BAP1* plays an essential role in maintaining genomic stability and is involved in transcription, DNA replication, homologous recombination repair, controlling cell death, and remodeling chromatin [30,34,35]. *BAP1* encodes a deubiquitylase and is involved in the regulation of H2A-Ub in the repressive group deubiquitinase Complex (PR-DUB) [30]. *BAP1* regulates chromatin accessibility by deubiquitylating INO80 via H2A-Ub. Through this, *BAP1* ensures genomic stability and efficient DNA replication, and therefore suppresses cancer development [30,36]. Since *BAP1* has been identified as a key tumor suppressor, it is a hopeful therapeutic target but has been found to be a complex target that is resistant to many current forms of therapy [30]. Clinical trials [NCT03830229, NCT03654833] are currently studying the role of *BAP1* [60,61]. Loss of *BAP1* impairs homologous recombination repair, making tumors more susceptible to PARP inhibitors [37]. *BAP1* deficiency also leads to the upregulation of *EZH2*, providing a target for potential therapeutic methods. *EZH2* inhibitors are currently being investigated for *BAP1* deficient cases of mesothelioma [38]. The *EZH2* inhibitor tazemetostat was tested in a clinical trial [NCT02860286] for its efficacy [37–39]. The trial results found that at 12 weeks there was a 54% disease control rate. However, no complete responses were observed in the trial [39]. Loss of *BAP1* impairs homologous recombination repair, making tumors more susceptible to synthetic lethality from PARP inhibition. In preclinical models, *BAP1* deficiency also leads to upregulation of *EZH2*, histone deacetylases (HDACs), and immune checkpoint molecules such as *PD-1*, *PD-L1*, and *LAG3*, providing multiple potential therapeutic targets. The *EZH2* inhibitor tazemetostat is currently being investigated in *BAP1*-inactivated mesothelioma (e.g., NCT03830229) [60]. While early-phase studies showed a disease control rate of 54% at 12 weeks, complete responses were not observed, suggesting that biomarkers beyond just *BAP1* may need to be explored for therapeutic treatment [39]. Many of the therapeutic treatment strategies involving *BAP1* remain largely preclinical but some provide future directions that may have promising results [37].

4.5. Hippo Signaling and NF2 Mutation

NF2 gene mutations were the second most common in our cohort with 15.19% of patients presenting *NF2* mutations. Similarly, another study found 19% of patients with the *NF2* gene mutation in another sample [33]. As stated earlier, *NF2*, also known as Merlin, is involved in the regulation of cell proliferation and the Hippo signaling pathway [27,28,31]. *NF2* regulates the downstream Hippo pathway via association of *LATS1*/*LATS2* which causes the suppression of *YAP* and *TAZ*, which are proteins associated with cell growth. Clinically, *YAP*/*TAZ* activation is linked to poorer outcomes in mesothelioma patients, making it a potential option for targeted therapy [40]. The mutation of *NF2* can lead to the hyperactivation of *YAP* and therefore leads to uncontrollable cell proliferation and tumor growth [31,41–43]. Beyond *NF2*'s role in *LATS1*/*LATS2*, *NF2* may also directly interact with transcription factor *TEAD4*, which is also involved in the Hippo signaling pathway [43]. This direct association can offer an alternative route to Hippo signaling deregulation in peritoneal mesothelioma.

YAP, *TAZ*, and *TEAD4* inhibitors such as IAG933 are phase I clinical trials [NCT04857372] for mesothelioma patients [43,45]. This trial is investigating the efficacy of disrupting the *YAP* pathway and treating the Hippo signaling pathway [44]. Focusing on the targeting of the *NF2* gene mutations and Hippo pathway could be an effective way in treating and slowing the progression of peritoneal mesothelioma [31,44].

4.6. p53 Pathway

The third most common mutation in our cohort occurred in the *TP53* gene with 9.3% of the patients presenting a mutation. This is consistent with other literature results that found the mutation rate for *TP53* ranges from around 8-14.6% [33,41]. *TP53* encodes the p53 protein, a transcription factor that is often referred to as the "guardian of the genome", and is responsible for responding to DNA damage by aiding cell cycle arrest, senescence, or apoptosis [41,46]. Loss of *TP53*, and therefore p53, function disrupts cell cycle regulation and leads to genomic instability and uncontrolled cell

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proliferation and tumorigenesis [33]. In mesothelioma, *TP53* is not the only mutation that can disrupt the p53 pathway. Alterations in checkpoint kinases, like *CHEK2*, and negative regulators, such as MDM2, can alter the p53 pathway [47,48]. In our cohort, *CHEK2* mutations were observed in metastatic tumors, which is consistent with literature that states *CHEK2* and *TP53* mutations have critical roles in tumor suppression. In other types of cancer, *CHEK2* and *TP53* mutations have linked expression patterns and frequently co-occur, which reinforces that disruption in the p53 pathway can alter DNA damage response [48]. For example, in a study *CHEK2* and p53 status was explored in 196 gastric cancer patients [47]. Results found that *CHEK2* mutations and p53 status are correlated, ultimately suggesting that there is an interplay between the two DNA damage response components [47]. So, in mesothelioma, damage or loss of the p53 pathway can arise from direct mutations of *TP53*, mutations in checkpoint kinases (i.e. *CHEK2*), or the amplification or overexpression of p53 negative regulators (i.e. MDM2).

Regarding potential therapeutic interventions for *TP53* mutations, MDM2 inhibitors can restabilize the p53 pathway. For *TP53* wild-type tumors, MDM2 inhibitors can stabilize and reactivate p53. In a clinical trial [NCT01877382], an MDM2 inhibitor called milademetan has been explored and results show that inhibition of MDM2 could be a possible method to restabilizing the p53 pathways and suppressing tumor growth activity [47]. In addition, WEE1 inhibition is being clinically researched [NCT01164995, NCT02448329] in p53 mutated cells [49,62,63]. Clinical trial results [NCT01357161] have shown that adavosertib, a WEE1 inhibitor, has anti-tumor activity in *TP53* mutated tumors [50,51,64,65]. These observations highlight the p53 pathway as a critical component of mesothelioma biology. The p53 pathway should be further clinically explored as a therapeutic target for peritoneal mesothelioma.

4.7. Co-occurrence and Mutual Exclusivity Patterns

The analysis of our cohort presented several patterns in gene co-occurrence. There were statistically significant results between the *BAP1* and *PBRM1* (n=19; p<0.001) and *LATS1* and *LATS2* (n=5; p<0.001) genes. *BAP1* and *PBRM1* are associated with chromatin remodeling and DNA damage repair and the mutation of these genes concurrently could disrupt proper gene expression [41]. We also observed significant co-occurrence with the *LATS1* and *LATS2* (n=5; p<0.001) genes. *LATS1*/*LATS2*, tumor-suppressor kinases, both have significant roles in the Hippo signaling pathway [31,42–44]. In the Hippo signaling pathway, *NF2* activates *LATS1*/*LATS2* which then phosphorylates and deactivates *YAP* and TEADs, leading to uncontrolled cell proliferation and tumorigenesis [31,43,44]. However, in contrast, new results have also found that *NF2* can also directly interact with *TEAD4*, rather than via *LATS1*/*LATS2* and *YAP* [43]. Literature found that *NF2* and *TEAD4* directly interact via *NF2* interacting with the FERM domain and C-terminal tail of *TEAD4* [43]. This means that *NF2* can decrease the stability of *TEAD4* without interacting with *LATS1*/*LATS2* and *YAP* [43]. Therefore lack of *NF2* can stabilize *TEAD4* even if the *LATS1*/*LATS2* and *YAP* portion of the pathway is still intact [43]. Thus, the *LATS1*/*LATS2* co-occurrence may suggest that in order to uphold TEAD activity, there is genomic selection for loss of *LATS* kinase function. Although our sample size is small, suggesting that further research would need to be conducted to support the conclusion that both *NF2* loss or *LATS1*/*2* loss can lead to TEAD activation [28,43].

The dual deactivation of *LATS1*/*LATS2* likely still disrupts the Hippo signaling pathway and promotes uncontrolled cell proliferation and tumorigenesis. In addition, co-occurrence was observed with *BAP1* and *LATS1* (n=6; p=0.013) and *SETD2* (n=17; p= 0.003). *LATS1* and *PBRM1* (n=3; p=0.035) and *PBRM1* and *KMT2D* (n=2; p=0.014) genes also had a statistically significant co-occurrence pattern. These patterns suggest a cooperative role in tumorigenesis and mesothelioma growth [52].

In our cohort, we observed only one statistically significant mutually exclusive co-occurrence between *BAP1* and *TRAF7* (n=0; p<0.001). Due to the fact that these genes are mutually exclusive, it is likely that these genes were never mutated in the same tumor concurrently. *BAP1* mutations are frequently associated with chromatin pathway disruption and malignant forms of peritoneal mesothelioma [29,30,53]. *TRAF7* is a component in a separate pathway than the pathway *BAP1* uses,

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suggesting why it may be mutually exclusive to *BAP1*. *BAP1* and *TRAF7* being mutually exclusive suggests that there are alternative mutations, such as in *TRAF7*, to promote the cell proliferation and tumorigenesis in mesothelioma [54]. These mutually exclusive patterns within the chromatin remodeling and Hippo pathways could be used to inform future treatment and targeted therapeutic strategies.

4.8. Primary vs. Metastatic Mutation Patterns

In our cohort study, we also compared and looked at patterns between primary and metastatic mutations. Of all the statistically significant results, a majority of the gene mutations were found in metastatic tumors. Mutations in the following genes were only found in metastatic tumors: *CHEK2* (n=2; p=0.0187), *SRSF2* (n=2; p=0.0188), *PPP2R1A* (n=2, p=0.199), and *CARM1* (n=2, p=0.0303). Mutations within the *PBRM1* gene were observed in both metastatic and primary tumors. *PBRM1* mutations were numerically more common in primary tumors (n=12) than in metastatic tumors (n=6). Although, due to the smaller size of the metastatic group meant that a larger proportion of the metastatic tumors in our cohort carried *PBRM1* mutations in total. These patterns suggest that the enrichment of *CHEK2*, *SRSF2*, *PPP2R1A*, and *CARM1* may occur after or during metastasis. While the enrichment of *PBRM1* may occur prior to metastasis. These enriched genes all play a role in tumor progression. *CHEK2*, a tumor-suppressor gene, is relevant in cell cycle regulation and loss of its function can lead to improper cell proliferation [55]. *SRSF2* is involved in splicing events and enrichment of this gene may lead to altered RNA processing [56]. *PPP2R1A* is an important factor in DNA damage/repair [57]. According to literature, enrichment of *PPP2R1A* and many other genes can lead to tumorigenesis and lead to cancer progression [58]. *CARM1* is an arginine methyltransferase protein that is responsible for steps within the RNA production process [59]. In addition to the mutations found in metastatic tumors, we also observed a mutation in *TPM1* (n=2, p=0.0230) only in primary tumors. The association of these mutations with metastatic tumors presents the possibility that they are needed or contribute to the dissemination capacity of the peritoneal tumor cells. Although, these associations require further validation and study.

4.9. Study Limitations

This cohort study has several limitations that must be considered when interpreting findings. The AACR GENIE dataset lacks patient outcome measures such as overall or progression-free survival, limiting the ability to correlate genetic alterations with clinical outcomes. The dataset lacks measurement of patient clinical outcomes such as survival or progression free survival. Without access to endpoint data we cannot directly connect or draw conclusions about patterns in prognosis and treatment. Patient treatment histories are also not included in the dataset. This makes it difficult to assess if patients had genomic alterations or resistance or sensitivity to therapies. It is also impossible to tell if some of the gene mutations had arisen due to prior treatments. The cohort size of the dataset is another limitation. The relatively small number of cases for datasets on peritoneal mesothelioma limits statistical analysis. This makes it difficult to detect rare cases and establish associations. Inability to track tumor evolution over time and inability to compare primary and metastatic tumors from patients proved as another limiting factor. These serially collected samples, such as the matching of primary and metastatic tumors from the same patients, limited our ability to determine true driver mutations from secondary non-contributory mutations acquired during tumorigenesis. In addition, the GENIE database combines data from multiple institutions that use different sequencing platforms. So, it is inevitable that there could be some technical variability that could impact the reported and analyzed mutation frequencies. There is also a possibility that the dataset used contains multiple tumor samples from the same patient. Although, prior evaluations suggest that this would have minimal effect on overall trends seen in the data. Since we used genomic data, we cannot evaluate and capture non-genetic driving forces, such as microenvironmental factors, in the progression of peritoneal mesothelioma. There was also a lack of transcriptomic and miRNA data in our used GENIE dataset. Even without coding mutations, microRNA regulation and gene

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overexpression strongly influence tumor biology. We were unable to coordinate gene activity with mutation status due to the inability to analyze these molecular layers. Transcriptomic data is important for understanding peritoneal mesothelioma and gene overexpression. Without this data, we were unable to link downstream pathway activation to mutation status or actual gene expression. Similarly, our ability to explore epigenetic regulation in tumor progression and initiation was limited due to the fact that no DNA methylation data was available to us during this study. In future studies, incorporating and using DNA methylation data can provide a deeper understanding biologically and can have an impact on prognosis, treatment, and future research. Additionally, the GENIE database groups all histologic subtypes of peritoneal mesothelioma (epithelioid, sarcomatoid, and biphasic) together. Without specific subtype data, we could not analyze certain genomic alterations and enrichments that are found in particular morphologic variants. There was also a lack of immunohistochemistry data. This meant we could not examine how genetic changes translate cause differences in protein expression. Taking these constraints into account, our analysis can offer insight into the mutational and alterations in pathways such as the *BAP1* and chromatin, Hippo signaling, and p53 pathways. These results can help us characterize and understand peritoneal mesothelioma, hopefully laying the groundwork for future studies and clinical research for new therapeutic intervention.

5. Conclusions

This study provides a comprehensive analysis of the genomic mutational landscape of peritoneal mesothelioma using the AACR Project GENIE database. Recurrent genomic alterations were identified in *BAP1*, *NF2*, *TP53*, and *SETD2*. In addition, there were potential therapeutic target within the chromatin remodeling, Hippo signaling, and p53 pathways. Demographic patterns were also analyzed and observed, and co-occurrence and mutually exclusive patterns highlighting distinct genomic patterns. The findings expand the current genomic insight for peritoneal mesothelioma which may guide future research, clinical trial design, and targeted therapeutic intervention.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available from the AACR GENIE Database at https://genie.cbioportal.org/ (accessed on 6 February 2025).

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Abbreviations

The following abbreviations are used in this manuscript:

AACR	American Association for Cancer Research
ASR	Age-Standardized Rate
BAP1	BRCA1-Associated Protein 1
CARM1	Coactivator-Associated Arginine Methyltransferase 1

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CDKN2A	Cyclin-Dependent Kinase Inhibitor 2A
CDKN2B	Cyclin-Dependent Kinase Inhibitor 2B
CHEK2	Checkpoint Kinase 2
CNA	Copy Number Alterations
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
EZH2	Enhancer of Zeste Homolog 2
FDR	False Discovery Rate
GENIE	Genomics Evidence Neoplasia Information Exchange
HDAC	Histone Deacetylase
H2A-Ub	Monoubiquitinated Histone H2A
LATS1	Large Tumor Suppressor 1
LATS2	Large Tumor Suppressor 2
LOH	Loss of Heterozygosity
MCL1	Myeloid Cell Leukemia 1
MDM2	Mouse Double Minute 2 Homolog
MPM	Malignant Peritoneal Mesothelioma
NF2	Neurofibromatosis Type 2
PARP	Poly (ADP-ribose) Polymerase
PBRM1	PolyBromo 1
PPP2R1A	Protein Phosphatase 2 Scaffold Subunit Alpha
SETD2	SET Domain Containing 2
SF3B1	Splicing Factor 3B subunit 1
SRSF2	Serine and Arginine Rich Splicing Factor 2
TAZ	Tafazzin
TEAD4	TEA domain transcription factor 4
TERT	Telomerase Reverse Transcriptase
TMB	Tumor Mutational Burden
TPM1	Tropomyosin 1
TP53	Tumor Protein p53
TRAF7	TNF Receptor-Associated Factor 7
KMT2D	Histone-Lysine N-Methyltransferase 2D
WEE1	WEE1 G2 checkpoint kinase
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing
WT1	Wilms' Tumor 1
YAP	Yes-Associated Protein

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