



MOLECULAR CHARACTERISATION OF CANCER-ASSOCIATED GENE MUTATIONS AND THEIR POTENTIAL FUNCTIONAL CONSEQUENCES

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ABSTRACT

The mutations associated with cancer may affect genomic stability, cancer risk, and clinical outcomes that are associated with DNA repair genes. BRCA1 and BRCA2 are especially notable as genetic variants in these genes are strongly linked with hereditary breast and ovarian cancers. In this study, we attempted to describe the distribution of BRCA1 and BRCA2 variants at the molecular level and assess their potential functional and clinical implications from the available variant classifications. A secondary bioinformatics analysis was done on a data set with 2000 cancer associated variant records. Frequencies, percentages, cross-tabulation and chi-square were used to analyse molecular characteristics such as distribution of genes, type of mutations, genomic annotation and clinical significance. Variants in BRCA2 were more common than variants in BRCA1. Single nucleotide variants were the most prevalent type of mutation, followed by deletions, and duplications, microsatellite variants and insertions and indels were less common. There were significant associations between gene identity and type of mutation, and between gene identity and clinical-significance classification. Deletions, duplications, insertions, indels, and microsatellite variants had a more uniform distribution of pathogenic related classifications, while the single nucleotide variants had a more diffuse distribution among the different classifications of pathogenic, benign, conflicting, and uncertain. The results suggest that BRCA1 and BRCA2 have different molecular and clinical-significance profiles. Combining mutation type with the type of variant could enhance interpretation of cancer associated alterations, aid molecular diagnosis and cancer-risk assessment, and aid the future work in precision oncology.

Keywords: BRCA1, BRCA2, cancer-associated mutations, molecular characterisation, clinical significance



1. Introduction

Cancer arises because of the gradual accumulation of genetic and molecular changes, which impair the normal regulation of cells and lead to uncontrolled growth, survival and progression of the disease. These changes include mutations in genes associated with cancer which can affect DNA repair, regulation of the cell cycle, apoptosis, signalling and genomic stability. Therefore, understanding the molecular features of such mutations is important to identify disease related genetic patterns and to clarify the potential biological impact of such mutations. Large-scale cancer genome analyses have revealed that the contribution of driver and passenger mutations to the overall molecular profile of malignancy can be very different, depending on both genes and tumour type (Kumar et al., 2020). Recent developments in "functional genomics" have also enhanced the capacity to study disease-related variants and the potential effect of each single genetic defect on cellular processes (Kim et al., 2024). The systematic functional assessment of cancer associated mutations using high throughput genome editing has also helped to better interpret genetic variants (Kim et al., 2022).

BRCA1 and BRCA2 are two of the best-studied cancer predisposition genes, due to their importance in genomic integrity. Both genes are involved in DNA damage repair, and the repair processes can be disrupted with pathogenic changes leading to a higher risk of breast, ovarian and other types of cancer. BRCA1 has regions of interest such as its C-Terminal BRCT domain, and mutations can disrupt protein interactions and DNA repair functions, affecting the initiation and progression of cancer and potential responses to treatment (Ismail et al., 2024). Additionally, germline and somatic mutations in BRCA1/2 have been extensively linked to the risk of hereditary breast and ovarian cancer, underscoring the critical significance of discriminating between pathogenic and non-pathogenic or variants of uncertain significance (VUS) (Pourmasoumi et al., 2024). In addition, structural changes and other molecular events of potential therapeutic significance have been revealed by whole-genome investigations of breast cancer, which further highlights the importance of detailed genomic characterisation (Al Assaad et al., 2024).

Molecular characterisation of cancer associated variants encompasses several genomic features such as gene, type of mutation, location on the chromosome, reference and alternate alleles and reported clinical interpretation. These methods have been used in various types of tumor to discover frequent molecular characteristics and clinically important changes. Genomic analysis has uncovered possible targets for therapy in gallbladder carcinoma (Giraldo et al., 2022), and genomic analysis of cervical adenocarcinoma has shown how genomic data can be used to identify biologically distinct groups of disease (Giannella et al., 2022). In odontogenic cysts and tumours, similar studies have highlighted the role of alterations at the level of genes in the development of the tumour and its biological behaviour (Gomes et al., 2023). Molecular profiling has also yielded valuable information on the unique histological and genetic properties of early onset colorectal cancer (Lawler et al., 2024).

The nature of the effects of genetic variants on function and clinical outcomes is also relevant, as not all genetic variants are biologically significant. Molecular diagnostics are quickly becoming a key tool for personalized cancer management, allowing for the identification of alterations that are linked to prognosis, therapeutic response, and targeted treatment opportunities (Riedl et al., 2024). The molecular classification of HER2+ breast cancer has also proven to be a good example of how genomic differences can be used to direct treatment (Li et al., 2024a). Besides DNA mutations, there are other molecular biomarkers such as non-coding RNAs which play a role in the detection and molecular assessment of cancer, further emphasizing the need for integrated molecular evaluation (Toden & Goel, 2022). Recent progress in cancer diagnostics using biosensors also underscores the importance of assessing tumours at multiple targets to better capture tumour heterogeneity (Cao et al., 2024).

Still, interpreting cancer associated genetic variants is difficult because there are many variants of uncertain significance or conflicting clinical interpretations. Therefore, a systematic comparison of the different types of mutations, of the distribution of genes, and of the clinical utility may be helpful



in providing insight into the potential functional consequences of the mutations and for improved molecular interpretation.

Objectives

- To characterise the molecular distribution and mutation patterns of cancer-associated variants in BRCA1 and BRCA2 genes.
- To compare the frequency and types of genetic variants identified in BRCA1 and BRCA2.
- To evaluate the potential functional and clinical consequences of identified variants based on their reported significance and pathogenicity classifications.

2. Materials and Methods

2.1 Study Design

The approach used in this study was a secondary data, bioinformatics, retrospective study to describe genetic variants associated to cancer and explore their possible functional/clinical implications. Variants in the BRCA1 and BRCA2 genes were analysed as these genes have been widely studied for their role in hereditary cancer susceptibility and DNA repair mechanisms. There was no usage of any patient recruitment procedures or primary biological samples. The research was planned as a descriptive and comparative genomics study based on information on variants available publicly.

2.2 Data Source and Study Dataset

A cancer-associated genetic variant dataset was publicly available, and these were analysed (Nagendra, 2025). A working data set comprising of 2000 variant records and 43 variables was used for this current study. There were 715 BRCA1 and 1,285 BRCA2 variants included in the data set. These records were each a reported genetic variant, as well as molecular, genomic, phenotype, review, and clinical-significance data. The data set contained both the GRCh37 and GRCh38 genome assemblies.

2.3 Variables Included in the Analysis

The most important variables that were chosen for analysis were the gene symbol, gene identifier, HGNC identifier, mutation type, variant name, chromosome, genomic start position, genomic end position, reference allele, alternate allele, cytogenetic location, phenotype information, origin, genome assembly, clinical significance, review status, and number of submitters. There was a focus on Gene Symbol, Type, and Clinical Significance, which were the most pertinent variables to aid in the comparison of the mutation patterns and their reported clinical consequences. Other annotation fields were employed to specify the position in the genome and the identity of the variants.

2.4 Data Preparation and Quality Assessment

The dataset was then loaded into the analytical context and analysed for dimensions, dimensional consistency, variable names, missing information, duplicate information and category structure. The variant records were kept as they were with the molecular and clinical information they had. Records for the genes BRCA1 and BRCA2 were isolated for comparison. The variants were categorized as single nucleotide variants, deletions, duplications, microsatellite variants, insertion or indels and were standardized as per the existing categories in the data. The classifications of clinical significance were also kept as per original ClinVar designation.

2.5 Molecular Characterisation of Genetic Variants

Molecular characterisation was done by analysing the distribution of variants based on the mutated gene and the type of mutation. To determine differences in the composition of variants in BRCA1 and BRCA2, the major classes of mutations were compared. Genomic location, cytogenetic position, genomic coordinates, reference and alternate alleles and variant identifiers were also used to assess



genomic characteristics. Single nucleotide variants (SNVs), deletions, duplications, insertions, microsatellite variants (MSVs), and indels (deletions and/or insertions) were summarized and compared between the two genes.

2.6 Assessment of Potential Functional and Clinical Consequences

The identified variants were assessed on their potential consequences mainly using the Clinical Significance variable. Pathogenic, likely pathogenic, pathogenic/likely pathogenic, benign, likely benign, benign/likely benign, uncertain significance, and conflicting pathogenicity were all considered variants. These categories were used as measures of likely clinical and functional importance of the variants. Since no experimental measurement of protein dysfunction was present in the data set, the consequences of protein dysfunction were limited to known variant classification and available molecular annotation.

2.7 Statistical Analysis

The genomic data were summarised using descriptive statistics. Frequencies and percentages were used for categorical variables. Cross-tabulations were used for the comparisons between the distributions of BRCA1 and BRCA2 variants, mutation types and clinical-significance categories. Chi-square test of independence was used to determine that the distribution of mutation-type and clinical-significance classification of the two genes, BRCA1 and BRCA2, were not significantly different. A p value of < 0.05 was considered statistically significant. It was decided that analyses should not be predictive machine-learning models and should be descriptive and comparative.

2.8 Data Visualisation

The mutation landscape was graphically presented to facilitate easy understanding. The distribution of BRCA1 and BRCA2 variants and the frequency of the major types of mutations was displayed in bar charts. Clinical-significance categories of the two genes were compared using a stacked bar plot. Relationship between the mutation type, gene and pathogenicity classification was visualized using a heatmap. These visualisations were designed to be used alongside the tabulated results, as there was no additional numerical data provided in the text.

3. Results

3.1 Overall Characteristics of the Genetic Variant Dataset

A total of 2,000 variant records for BRCA1 and BRCA2 were analysed. BRCA2 was the most prevalent (BRCA1 was slightly more than a third). There were 1001 unique Variation IDs. Most of the records were of germline origin with a lower percentage of both germline and somatic origin. The genome assemblies GRCh37 and GRCh38 were the most common used for records. An overview of the dataset is provided in Table 1 and the distribution of BRCA1, and BRCA2 records is shown in Figure 1.

Table 1. General characteristics of the analysed cancer-associated variant dataset

Characteristic	Category	n	%
Total records	All variants	2,000	100.0
Gene	BRCA1	715	35.8
	BRCA2	1,285	64.3
Unique variants	Variation IDs	1,001	—
Origin	Germline	1,928	96.4
	Germline/somatic	72	3.6
Genome assembly	GRCh37	1,000	50.0
	GRCh38	999	50.0
	Not specified	1	<0.1

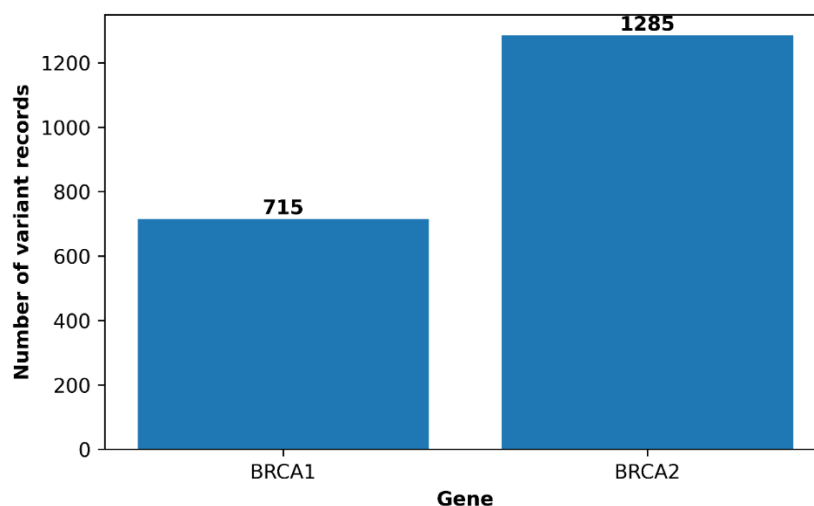


Figure 1. Distribution of BRCA1 and BRCA2 variant records

Figure 1 shows the predominance of BRCA2 variant records in comparison with BRCA1.

3.2 Distribution of Molecular Mutation Types

Six major types of mutations were found. In both genes, the most common molecular change was a single nucleotide variant, and deletion was the second most common change. Duplications and microsatellite variants were relatively underrepresented, in contrast to insertions and indels which were relatively small. The number of genes distributed in each is given in Table 2 and compared graphically in Figure 2.

Table 2. Distribution of mutation types according to BRCA1 and BRCA2

Mutation type	BRCA1, n (%)	BRCA2, n (%)	Total, n (%)
Single nucleotide variant	480 (67.1)	910 (70.8)	1,390 (69.5)
Deletion	138 (19.3)	225 (17.5)	363 (18.2)
Duplication	32 (4.5)	68 (5.3)	100 (5.0)
Microsatellite	32 (4.5)	54 (4.2)	86 (4.3)
Insertion	19 (2.7)	16 (1.2)	35 (1.8)
Indel	14 (2.0)	12 (0.9)	26 (1.3)
Total	715 (100.0)	1,285 (100.0)	2,000 (100.0)

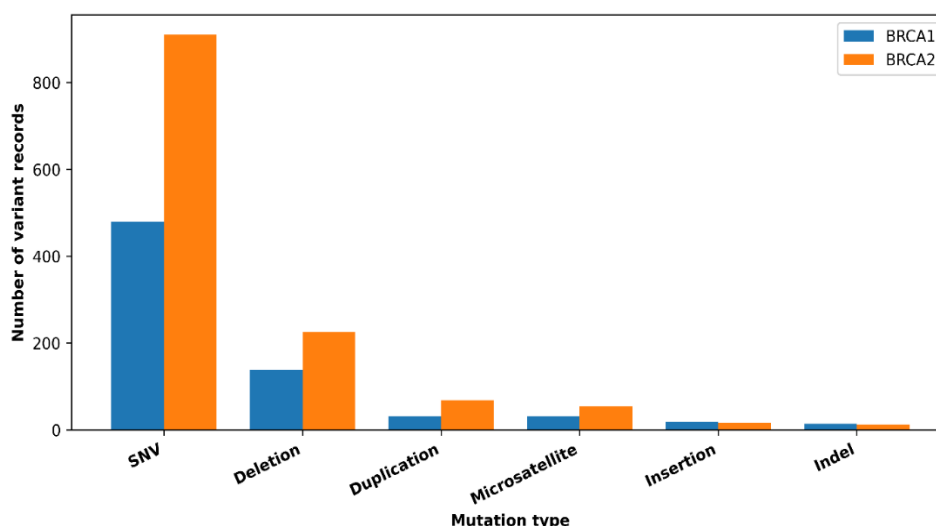


Figure 2. Mutation-type distribution according to BRCA1 and BRCA2



As illustrated in Figure 2, the overall molecular profiles of the two genes were dominated by single nucleotide variants, although differences were observed in the relative proportions of less common mutation types.

3.3 Clinical Significance of BRCA1 and BRCA2 Variants

The clinical significance of the variants was reported to be quite wide ranging between the variants. Pathogenic variants were the most predominant single classification followed by variants with conflicting classifications of pathogenicity. However, another large category of benign variants was identified, as were much fewer variants of uncertain significance, likely benign, and likely pathogenic variants. The full profile of clinical significance of each gene is given in Table 3.

Table 3. Clinical-significance classifications of BRCA1 and BRCA2 variants

Clinical significance	BRCA1, n (%)	BRCA2, n (%)	Total, n (%)
Pathogenic	359 (50.2)	515 (40.1)	874 (43.7)
Conflicting classifications of pathogenicity	142 (19.9)	422 (32.8)	564 (28.2)
Benign	126 (17.6)	156 (12.1)	282 (14.1)
Uncertain significance	14 (2.0)	84 (6.5)	98 (4.9)
Pathogenic/Likely pathogenic	40 (5.6)	30 (2.3)	70 (3.5)
Benign/Likely benign	12 (1.7)	44 (3.4)	56 (2.8)
Likely benign	16 (2.2)	30 (2.3)	46 (2.3)
Likely pathogenic	6 (0.8)	4 (0.3)	10 (0.5)
Total	715 (100.0)	1,285 (100.0)	2,000 (100.0)

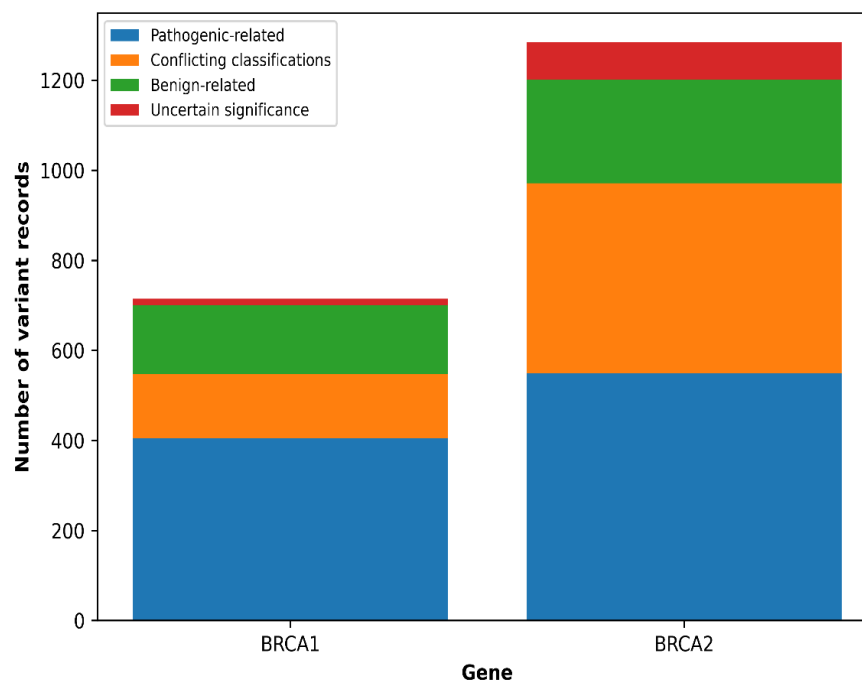


Figure 3. Clinical-significance profile of BRCA1 and BRCA2 variants

The contrasting clinical-significance profiles of BRCA1 and BRCA2 are further illustrated in Figure 3, where related pathogenic and benign classifications were combined for clearer graphical presentation.

3.4 Statistical Comparison of BRCA1 and BRCA2 Variant Profiles



The chi-square test showed that there was significant association between gene identity and mutation type ($P < 0.05$). A higher statistically significant correlation was also found between gene identity and clinical-significance classification. These results show that the distribution of the molecular mutations within the two genes and the clinical consequence profiles reported were not the same between BRCA1 and BRCA2. Summary of inferential results in Table 4.

Table 4. Chi-square analysis of mutation characteristics according to gene

Comparison	χ^2	df	p-value	Result
Gene $\times$ mutation type	11.343	5	0.045	Significant
Gene $\times$ clinical significance	89.215	7	<0.001	Significant

As reported in Table 4, both molecular mutation type and clinical-significance classification showed significant gene-specific variation.

3.5 Mutation Types and Potential Clinical Consequences

All detailed clinical classifications were regrouped in pathogenic-related, benign-related, conflicting and uncertain groups to create a better view of the potential consequences. Differences were found between the various types of mutation. Within the pathogenic-related group, the most common type of variation was deletion, duplication, insertion, indels and microsatellite variants. Single nucleotide variants, on the other hand, showed a highly variable distribution in pathogenic, benign, conflicting and uncertain classes. The distribution is given in Table 5.

Table 5. Mutation types according to grouped clinical-significance classification

Mutation type	Pathogenic-related, n (%)	Conflicting, n (%)	Benign-related, n (%)	Uncertain significance, n (%)
Single nucleotide variant	388 (27.9)	544 (39.1)	372 (26.8)	86 (6.2)
Deletion	339 (93.4)	10 (2.8)	4 (1.1)	10 (2.8)
Duplication	94 (94.0)	4 (4.0)	2 (2.0)	0 (0.0)
Microsatellite	72 (83.7)	6 (7.0)	6 (7.0)	2 (2.3)
Insertion	35 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Indel	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)

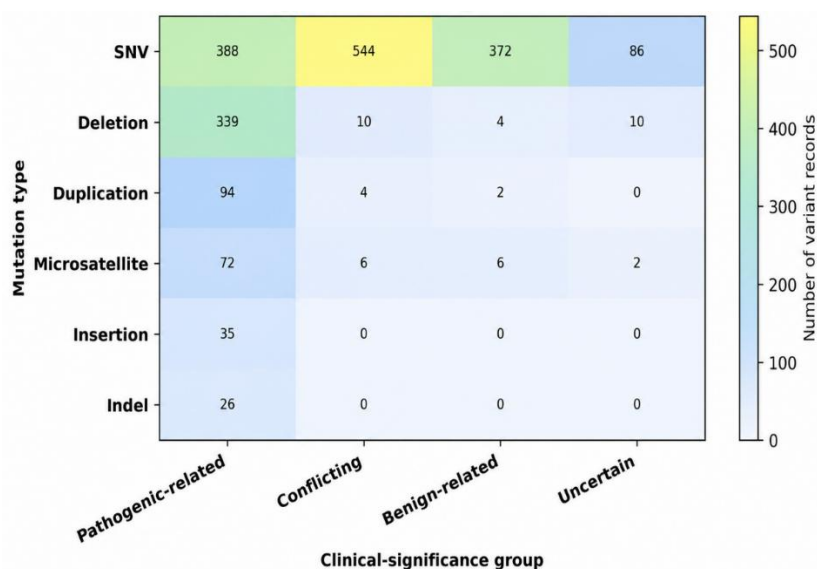


Figure 4. Heatmap of mutation types and clinical-significance groups

The correlation between molecular type of mutation and clinical significance grouped is represented



in Figure 4. This heatmap illustrates the enrichment of pathogenic related classifications in structural mutation categories and the relatively broad consequence spectrum of single nucleotide variants.

The overall results suggest that there are different molecular and clinically significant patterns in BRCA1 and BRCA2. Together, the results shown in Tables 1-5 and Figures 1-4 help to decipher the possible functional and clinical impact of the detected cancer associated variants.

4. Discussion

In the current study, 2,000 BRCA1 and BRCA2 variant records were characterized, and significant differences were observed with respect to both the distribution of the mutation types and clinical-significance profiles. BRCA2 variants were more common than BRCA1 variants and single nucleotide variants were the most common molecular variants in both genes analysed. The second most common class of alterations were deletions while duplications, microsatellite variants, insertions and indels were less common. This discovery reinforces the general idea that genes related to cancer have different patterns of molecular changes, and do not have the same spectrum of mutations. This molecular heterogeneity has been observed in other cancer types as well, with genomic and transcriptomic subtyping showing the presence of distinct molecular cancer types with different clinical features (Chen et al., 2024). Molecular classification strategies in gastric cancer have also shown that there is genomic variability that can be linked to clinically relevant disease phenotyping (Shi et al., 2024).

The statistically significant relationship between gene identity and mutation type suggests that BRCA1 and BRCA2 have different types of mutational profiles. This observation is in keeping with the findings of molecular changes that occur in cancer, which are highly diverse depending on the gene, the tumour type and the biological pathway. Molecular subtyping of gastric cancer has been linked to variations in tumour behaviour and clinical outcomes (Li et al., 2023), and molecular characterization of early-onset CRC has identified genomic features that may have prognostic and/or immunotherapeutic implications (Lu et al., 2023). In the same way, the drivers of heterogeneity have been shown in patient cohorts in endometrial carcinoma, suggesting that we should study the alterations of individual genes instead of cancer associated variants as one group (Weigelt et al., 2023). Different liver cancer genomic profiles have also been linked to immune-evasion mechanisms, further highlighting the biological implications of the distinct characteristics of liver cancer genomic signatures (Wong et al., 2022).

Another important degree of heterogeneity was found by clinical-significance analysis. The pathogenic-related classifications were more frequent among deletions, duplications, insertions, indels and microsatellite variants, while single nucleotide variants were more widely spread across the different classifications (pathogenic, benign, conflicting and uncertain). Such a pattern indicated that the type of molecular variant may play a role in the possible clinical consequences of cancer associated alterations. Similar molecular association with clinically relevant biological pathways has been reported for melanoma where pathway specific molecular changes were associated with therapeutic implications (Guan et al., 2023). Cancer related gene signatures of ferroptosis and cuproptosis have also been linked to the clinical implications and immune interactions in colorectal cancer (Li et al., 2022); angiogenesis associated molecular signatures have also been shown to correlate with the clinical characteristics and tumour immunity in gastric cancer (Qing et al., 2022).

The results also need to be studied in the context of the overall biology of tumour heterogeneity. In addition to the single gene changes, the genetic changes within the tumour microenvironment interact with other components, including those from the cellular and stromal compartments, and their functional consequences might be more complex than single gene changes. Cancer-associated fibroblasts have been reported to affect tumour biology, progression and therapeutic response in the different type of cancers including glioblastoma (Galbo et al., 2024), prostate cancer (Owen et al., 2022) and gastric cancer (Zhao et al., 2023). Moreover, experiments have shown that there is significant functional heterogeneity among tumour-derived populations of fibroblasts in the cancer microenvironment (Zhou et al., 2022). Single-cell and spatial analysis of the same cancers have also



identified complex molecular states in groups of senescence-related fibroblasts (Li et al., 2024b) and molecular landscapes of cells associated with fibroblasts have been correlated with clinical outcome and immunotherapy response in the case of ovarian cancer (Zou et al., 2022).

Nevertheless, the study has some limitations. Analysis was done by secondary variant record and no direct measurements of protein dysfunction, transcriptional effects or cellular phenotype were made. Thus, clinical-significance classifications were adopted as proxy measures for potential functional consequences, instead of functional validation. Future studies need to combine information regarding genomic variants with gene-expression profiles, protein function and experimental assays to elucidate the functional impact of ambiguous and conflicting variants and enhance the interpretation of cancer associated variants.

5. Conclusion

In this study, cancer-associated variants in the BRCA1 and BRCA2 genes were molecularly characterised, and their potential functional and clinical impacts assessed using a secondary genomic dataset. The analysis revealed that there were more BRCA2 variants than BRCA1 variants and that the most common type of mutation in both genes was single nucleotide variants. Other alterations included deletions, which were the second most frequent, and microsatellite variants, insertions and indels were less frequent. Substantial correlation with gene identity and type of the mutation suggested that BRCA1 and BRCA2 have different molecular mutation profiles. Further analysis of the identified mutations for clinical significance also showed significant differences in the level of importance predicted for the mutations. Single nucleotide variants had a more pervasive distribution between pathogenic, benign, conflicting and uncertain classifications, whereas deletions, duplications, insertions, indels and microsatellite variants were more likely to be pathogenic-related. These results indicate that the interpretation of cancer associated variants should consider both type of mutation and the gene context. The study also illustrates the utility of publicly available genomic information in uncovering clinically relevant patterns of mutations and molecular research on cancer. The findings are however based on current classifications of variants, not on laboratory evaluation of protein or cellular function. In the future, it will be necessary to integrate variant information with transcriptomic, proteomic and experimental functional data to facilitate interpretation of less confident variants and enhance their utility in cancer risk prediction, molecular diagnosis and precision oncology.

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