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Analysis of BRCA1 Gene Character in Families with a History of Breast Cancer

Miftahul Mushlih[1]*, Baiti Jennah[1]

1Jurusan Teknologi Laboratorium Medis, Fakultas Ilmu Kesehatan, Universitas Muhammadiyah, Sidoarjo 61215, Jawa Timur, Indonesia

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***Corresponding author:**
mif.mushlih@umsida.ac.id

Abstract

Breast cancer is one of the leading causes of cancer-related mortality among women worldwide and is strongly associated with hereditary mutations in the BRCA1 gene. This study aimed to identify the inheritance pattern and mutation profile of the BRCA1 gene in families with a history of breast cancer. A descriptive exploratory study was conducted from September 2024 to January 2025 at the Molecular Biology Laboratory, Faculty of Health Sciences, Muhammadiyah University of Sidoarjo. Three families with suspected hereditary breast cancer were recruited using purposive sampling. Pedigree analysis covering three generations was performed to assess inheritance patterns. Venous blood samples were collected for DNA isolation, followed by PCR amplification targeting a 359 bp fragment of the BRCA1 gene and DNA sequencing. Sequence alignment was conducted using BLAST against reference sequences from the NCBI GenBank database. The results identified BRCA1 gene mutations in three individuals from different families. The detected variants were c.2805delA, c.3280delC, and c.2612C>T. Two deletion mutations (c.2805delA and c.3280delC) were found in second-generation members of one family, while a substitution mutation (c.2612C>T) was identified in a second-generation individual diagnosed with breast cancer. Pedigree analysis supported an autosomal dominant inheritance pattern consistent with Hereditary Breast and Ovarian Cancer (HBOC) syndrome. The identified deletion mutations may lead to frameshift alterations and impaired BRCA1 protein function in DNA repair.

INTRODUCTION

Cancer is a disease characterized by the presence of abnormal cells that grow uncontrollably and have the ability to invade and spread between cells and tissues in the body. The aim of this study is to identify the inheritance of the BRCA1 gene in families with a history of breast cancer. The World Health Organization (WHO) lists cancer as one of the leading causes of death worldwide (Puspa Ningrum & Sri Ratna Rahayu, 2021). One of the most common types of cancer among Indonesian women is breast cancer, surpassing cervical cancer, which accounts for 24%. According to the 2023 Health Statistics Profile published by the Indonesian Central Bureau of Statistics, the prevalence of cancer in Indonesia has increased, particularly breast cancer, which accounts for approximately 66.37 cases (Hardianto et al., 2023).

Breast cancer is one of the most commonly found types of cancer in women worldwide and is the second leading cause of death among women after lung cancer (Hero Khairunnisa Syifa et al., 2021). In cases of this type of cancer, patients commonly present with complaints such as the presence of a palpable mass in the breast region, either unilaterally or bilaterally, which may be associated with pain or may be asymptomatic (Ketut and Kartika , 2022). A lump is often the initial sign of breast cancer and occurs due to the uncontrolled division of cells within the breast tissue, leading to the formation of a mass. Most cases originate in the lobules or the ducts that connect the lobules to the nipple (Asiah et al., 2019).

The gene mutation that is correlated with familial breast cancer is the BRCA1 (Breast Cancer 1) gene (Wayan et al., 2013). BRCA1 is located on chromosome 17q21, specifically on the short arm (p) of chromosome 17 at position 17q21.31, and it contains a multifunctional protein domain (Fu et al., 2022). Mutations in the BRCA1 gene are present in every cell of the body and are inherited from one generation to the next. Therefore, these mutations are associated with familial breast cancer. However, not everyone who inherits the BRCA1 gene mutation will develop cancer. In addition to genetic hereditary factors, environmental factors and lifestyle also influence an individual's cancer risk (Semmler, Reiter and Klein, 2019). In breast cancer, most BRCA1 gene mutations result in the production of abnormal or truncated BRCA1 proteins, preventing the formation of any functional protein from the gene copy. Consequently, the available protein is reduced, and since this protein plays a crucial role in repairing damaged DNA and correcting other gene mutations, its deficiency impairs these functions. When this mutation occurs, it can trigger uncontrolled cell growth and division, leading to tumor formation (Antoniou et al., 2020) A study conducted in Jordan concluded that positive mutations in the BRCA1 gene are one of the causes of breast cancer. Therefore, breast cancer services such as genetic counseling and early genetic screening are necessary. Previous research explained that carriers of the positive BRCA1 gene mutation have a high risk of developing breast cancer, estimated at 72%(Abu-Helalah et al., 2020).

The sequencing results from the study by Farid Cherbal at the Molecular Biology Laboratory, University of Science and Technology "Houari Boumediene" in Algiers, Algeria, revealed the following mutations in the BRCA1 gene: c.442-34C>T, c.1067A>G, c.2077G>A, c.2082C>T, c.2311T>C, c.2521C>T, c.2612>CT, c.2733A>G, c.3133A>G, c.3119G>A, c.3418A>G, c.3548A>G, c.4308T>C, and c.4837A>G. These sequencing variants are located in different exons (Cherbal et al., 2012).

METHOD

This study employed a descriptive exploratory research design conducted at the Molecular Biology Laboratory, Faculty of Health Sciences, Muhammadiyah University of Sidoarjo, from September 2024 to January 2025. The samples used were family samples suspected of having a hereditary history of breast cancer, confirmed through interviews and pedigree analysis or family lineage analysis with a history of inherited breast cancer. Ethical clearance was approved by Airlangga University under certificate number 0927/HRECC.FODM//VIII/2024. Sampling in this study was carried out using purposive sampling technique, with the population subjects being families with a hereditary/genetic history of breast cancer.

The samples used in this study were venous blood samples collected using a macro sampling technique with a volume of 3 cc. Sample collection was conducted at the homes of families with a history of breast cancer. Prior to sample collection, interviews were conducted to obtain family lineage data for detecting the inheritance of the BRCA1 gene in breast cancer. This data was then used to construct the pedigree.

This study began with pedigree analysis, which is an important step to detect the possibility of genetic inheritance in families with a history of breast cancer. The process started by conducting structured interviews with family members who have a history of breast cancer. These interviews were designed to gather detailed information on at least three generations of family lineage, including kinship relationships, gender, age, living or deceased status, and age at cancer diagnosis, particularly breast cancer. The collected data were then used to construct a pedigree chart using standard symbols(Bennett et al., 2008). The results of this pedigree analysis helped support molecular findings and strengthened the suspicion of a genetic predisposition to breast cancer within the family. Furthermore, the information obtained from the pedigree served as a basis for genetic counselling and consideration of further screening for high-risk family members. The collected blood samples were then subjected to DNA isolation to obtain pure DNA. After pure DNA was obtained, an optimization process was conducted to determine the appropriate annealing temperature for the PCR procedure.

The PCR process utilized primer designs Forward 5'-GAGGACAAAGCAGCGGATAC-3' and Reverse 5'-GCTGTAATGAGCTGGCATGA-3' (Algebaly, Suliman and Al-Qahtani, 2021). , targeting a sequence length of 359 bp. The reaction was carried out in a total volume of 40 µL, consisting of 20 µL PCR mix, 0.8 µL forward primer, 0.8 µL reverse primer, 10 µL pure DNA sample, and 8.4 µL ddH_2O. The PCR technique was performed using a thermocycler with several stages, including pre-denaturation at 94℃ for 10 minutes, denaturation at 94℃ for 1 minute, annealing at the previously determined temperature of 45.8℃ for 45 seconds, elongation at 72℃, and post-elongation at 72℃ for 5 minutes. A total of 35 cycles were used. The PCR products were then subjected to sequencing.

The sequencing process was carried out by sending the remaining PCR product to Tangerang, Banten, where it was processed at PT Genetika Science Indonesia. Sequencing is a molecular technique used to determine the specific and precise order of nucleotide bases in a target DNA fragment. The sequencing results were then subjected to alignment to identify the nucleotide sequence.

The alignment process was performed to compare the DNA sequences obtained from isolation and amplification with reference sequences to detect genetic mutations. In this study, sequence alignment was conducted after the DNA sequencing stage using bioinformatics software such as BioEdit or BLAST (Basic Local Alignment Search Tool). The DNA sequence data from patient samples were input into the software and then aligned with the reference sequence of the BRCA1 gene obtained from the NCBI GenBank database.

RESULTS AND DISCUSSION

Genetics plays a significant role in the development of certain diseases. This study began with pedigree analysis obtained through interviews with family members. The pedigree analysis in this study followed the standardized guidelines consistently recognized by the National Society of Genetic Counselors (NSGC) for recording genetic family health histories (Bennett et al., 2008). The results showed mutations in the BRCA1 gene in respondents who had not yet developed cancer but had a family history of breast cancer. Factors considered as indicators in this study included age, hormonal influences, lifestyle, and other genetic modifiers that could affect the phenotypic expression of mutations. Individuals carrying pathogenic BRCA1 gene mutations and with a family history are more likely to develop breast cancer at a younger age (Mavaddat et al., 2013). This study used samples showing clinical symptoms in individuals with a family history of breast cancer, consisting of three families and three individuals identified with BRCA1 gene characteristics. In Family 1, samples were collected from female family members, confirmed in the first generation (grandmother) who had breast cancer, which was inherited by one of her children who developed breast and ovarian cancer. In Family 2, samples were collected from female family members, confirmed in the first generation (grandmother) who had breast cancer and the second generation diagnosed with ovarian cancer. Germline mutations in the BRCA1 gene play a crucial role in increasing the risk of breast and ovarian cancers, known as Hereditary Breast and Ovarian Cancer (HBOC) syndrome (Bouras et al., 2023). In Family 3, samples were collected from female family members and one male family member, confirmed in the first generation (grandmother) who had breast cancer and passed it on to one of her children.

The examination of family relationships accompanied by inherited characteristics can facilitate the identification of the possible inheritance of a genetic disease

Family relationship examinations accompanied by inherited characteristics can facilitate the identification of possible genetic disease inheritance (Wolyniak et al., 2015). In Family 1, two individuals in the second generation experienced mutations at different sites, namely del3280C and del2805A, which demonstrates that these individuals inherited breast cancer from a family member in the first generation (mother), passing it on to their children (second generation). Mutations were also found in a member of Family 2, who had a mutation at site C2612T and had been diagnosed with breast cancer. This mutation was inherited from the first generation (mother) to her children. According to Rosen's study (2014), breast cancer is a genetic disease inherited in an autosomal dominant manner (Rosen & Pishvaian, 2014). . Individuals who inherit one mutant allele have an increased risk of developing breast cancer, and this inheritance pattern means that children of a parent who carries the mutation have a 50% chance of inheriting the mutant allele(Kuchenbaecker et al., 2017).

Lifestyle also plays an important role in reducing the risk of breast cancer, even though this disease is not contagious but rather caused by a combination of genetic and environmental factors. One lifestyle factor that has a significant impact is excessive alcohol consumption, which can increase the risk of breast cancer by elevating estrogen levels and causing DNA damage in cells (Colditz and Bohlke, 2014).Therefore, individuals with a genetic predisposition to breast cancer should maintain a healthy lifestyle

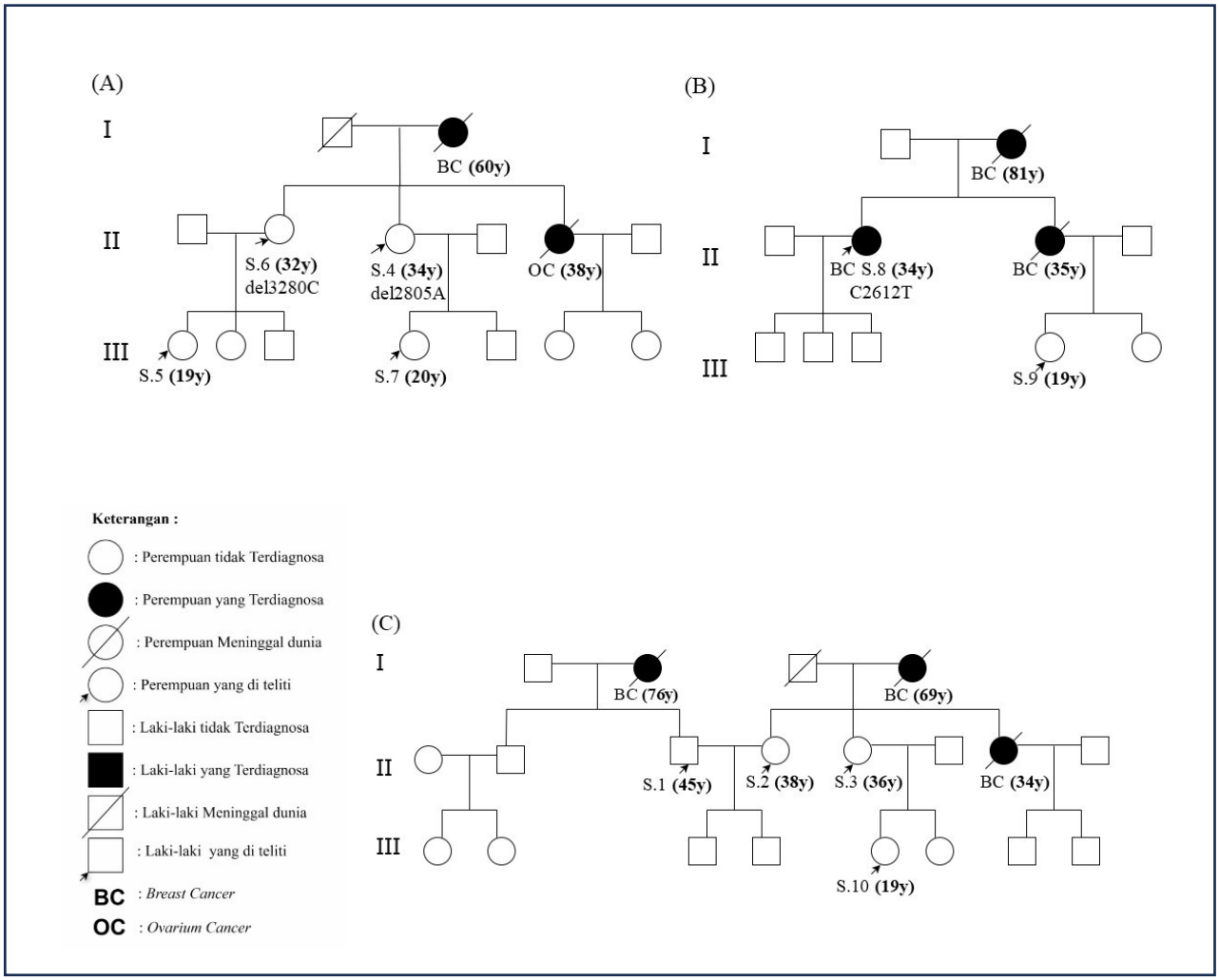

Figure 1. (A) Pedigree diagram of Family I (Family with cases of breast cancer and ovarian cancer in Lakarsantri District, Surabaya), (B) Pedigree diagram of Family II (Family with breast cancer cases in Krian District, Sidoarjo), (C) Pedigree diagram of Family III (Family with breast cancer cases in Bangil District, Pasuruan). **BC**: Breast Cancer, **OC**: Ovarian Cancer

The alignment results of the three samples (S4, S6, and S8) revealed different point mutations, which were analysed using three control nucleotide sequences or BRCA1 gene BLAST references (PQ399722, PQ399721, PQ399720). The purpose of this analysis was to determine whether changes in nucleotide bases indicate the presence of mutations. Figure 2 shows the alignment results obtained through BLAST. In all three samples, nucleotide base changes and deletions were observed. In sample S4 (indicated by a red box), an individual from Family 1, second generation (Figure 1(A)), showed a deletion at position 2805, specifically the loss of the purine base A. This indicates a BRCA1 gene mutation at position del2805A. In sample S6 (yellow box), also an individual from Family 1, second generation (Figure 1(A)), the alignment showed a deletion at position 3280, involving the loss of nucleotide C, indicating a BRCA1 mutation at del3280C. Meanwhile, sample S8 (blue box), an individual from Family 2, second generation (Figure 1(B)), showed a point mutation at position C2612T. Genetic mutations in the BRCA1 gene are a significant factor contributing to the risk of familial breast cancer. The BRCA1 gene plays a critical role in the repair mechanism of DNA double-strand breaks through homologous recombination repair, thereby maintaining genomic stability (Roy et al., 2012). Mutations that lead to BRCA1 protein dysfunction, such as deletions and insertions, can result in the accumulation of DNA damage, increasing the risk of breast cancer (Narod, 2010). A deletion mutation refers to the removal of one or more nucleotides from the DNA sequence. Deletions that are not in multiples of three can cause a frameshift mutation, which alters the entire codon reading frame after the mutation point, resulting in an abnormal or truncated protein(Venkitaraman, 2002).

A BRCA1 protein damaged by a deletion is unable to perform DNA repair functions effectively, thus increasing the potential for carcinogenesis (Chen and Parmigiani, 2018). Meanwhile, nucleotide substitution mutations, such as the C2612T mutation, may cause amino acid changes (missense mutations) that alter the structure of the BRCA1 protein. The functional impact depends on the location of the mutation and the type of substituted amino acid(Miki et al., 2020).

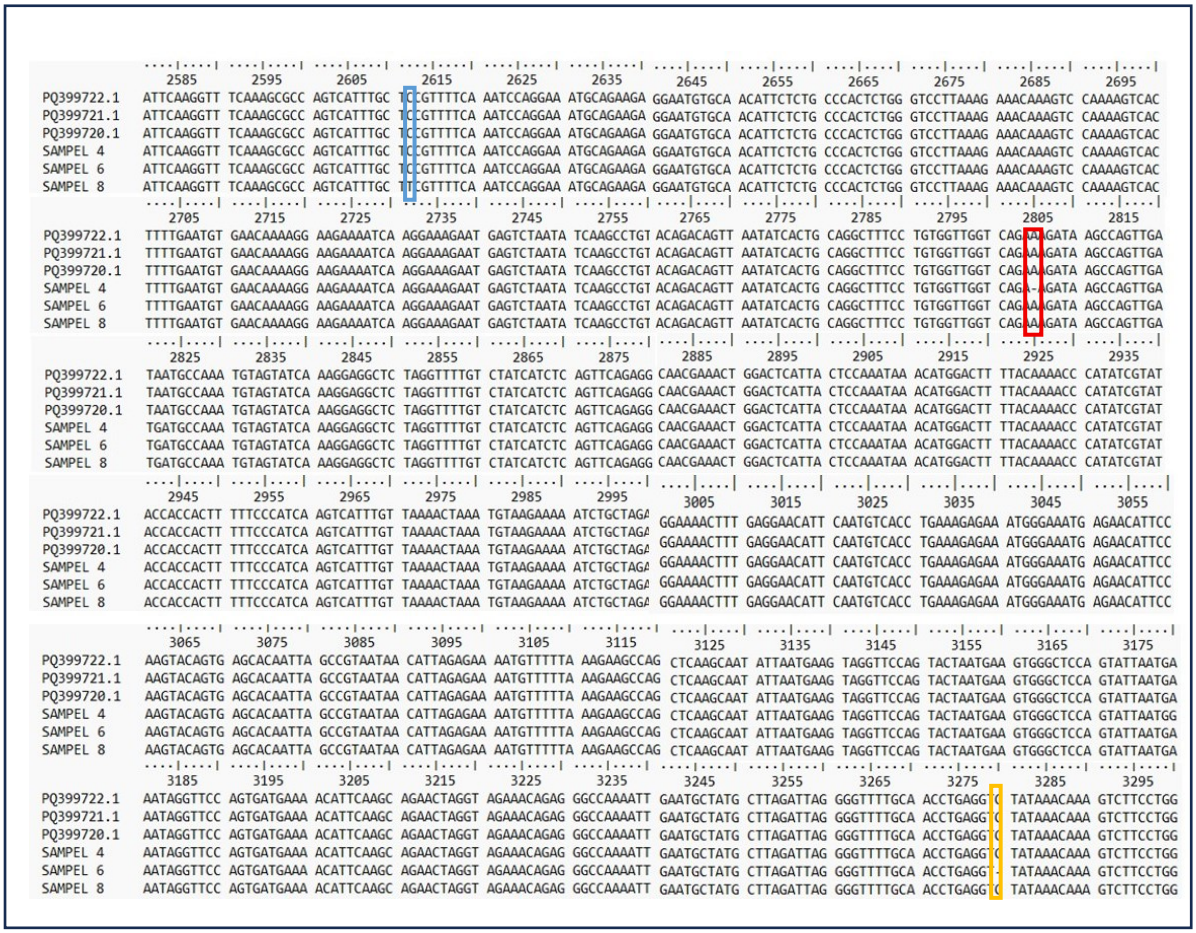

Figure 2. Alignment results of samples identified with mutations c.2612C>T, c.2805delA, and c.3280delC. (Red box S4: c.2805delA; Yellow box S6: c.3280delC; Blue box S8: c.2612C>T)

BRCA1 mutations in breast cancer among Saudi women are frequently found at the del2805A position, with a prevalence of 35% (Algebaly et al., 2021). In this study, however, a novel mutation point was identified at del3280C. A study by Yayan Wang (2018) involving a 33-year-old Chinese woman using sequencing techniques revealed a heterozygous deletion-insertion mutation in the BRCA1 gene (c.311_312delinsAGGTTTGCA), which led to a truncated BRCA1 protein due to interrupted synthesis. This finding aligns with the present study, where a woman under the age of 35 was found to carry a deletion mutation in the BRCA1 gene at position del3280C, potentially increasing the risk of breast cancer(Wang et al., 2018). In a study by Jeffrey N. on unilateral breast cancer cases, it was shown that considering family history, age of disease onset, and family structure influences the accuracy of breast cancer probability models. The study found that participants diagnosed before the age of 40 had significantly higher risk levels, consistent with this study's finding that an individual under the age of 40 was a carrier of a BRCA1 gene mutation(Weitzel et al., 2007).

BRCA1 is a tumor suppressor gene that functions to inhibit tumor growth and repair DNA. Genetic mutations in breast cancer occur in approximately 5% of cases annually in the United States. BRCA1 mutations increase the risk of developing breast cancer by four times (Romadhon, 2019). Family history is considered a major risk factor for breast cancer, accounting for approximately 5–10% of breast cancer cases. The presence of BRCA1 gene mutations can cause cells to grow uncontrollably, leading to cancer. These gene mutations can be inherited, which is why individuals with a family history are advised to undergo early screening (Zakia et al.,2021).

CONCLUSION

Based on the results of BRCA1 gene analysis in three samples from three different families, it can be concluded that two family members from Family 1 and one family member from Family 2 were identified as having BRCA1 gene mutations. The mutations occurred at positions del2805A, del3280C, and C2612T. The successful analysis of BRCA1 gene characteristics using the sequencing method can be used as an initial screening tool for individuals with a family history of breast cancer.

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