Identification of shared neoantigens in BRCA1-related breast cancer

Miss Lucksica Ruangapirom

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การหานีโอแอนติเจนที่เกิดขึ้นซ้ำในมะเร็งเต้านมที่เกี่ยวข้องกับยีนบีอาร์ซีเอวัน

น.ส.ลักษิกา เรืองอภิรมย์

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ลักษิกา เรืองอภิรมย์ : การหานีโอแอนติเจนที่เกิดขึ้นซ้ำในมะเร็งเต้านมที่เกี่ยวข้องกับยีนบีอาร์ซีเอวัน. (Identification of shared neoantigens in BRCA1-related breast cancer) อ.ที่ปรึกษาหลัก : ศ. ดร.อภิวัฒน์ มุทิรางกูร, อ.ที่ปรึกษาร่วม : อ. ดร.ฉัทชนันท์ ด้วงคำจันทร์

วัคซีนมะเร็งเฉพาะบุคคลที่ใช้ neoantigens ได้รับการพิสูจน์แล้วว่าปลอดภัยและสร้างภูมิคุ้มกันในผู้ป่วยมะเร็ง อย่างไรก็ตาม กระบวนการผลิตอาจมีค่าใช้จ่ายสูงและทำให้เกิดการรักษาล่าช้า การผลิตวัคซีนป้องกันมะเร็งพร้อมใช้ที่ผลิตจาก neoantigens ที่มีร่วมกันในมะเร็งชนิดชนิดนั้นๆอาจหลีกเลี่ยงปัญหาเหล่านี้ได้ การศึกษานี้กำหนดให้มะเร็งเต้านมที่กลายพันธุ์ของยีน *BRCA1* เป็นตัวเลือกสำหรับการหา neoantigens ที่มีร่วมกันเนื่องจากมีอาการทางคลินิกและความคล้ายคลึงกันของจีโนไทป์และฟีโนไทป์ซึ่งบ่งชี้ถึงการกลายพันธุ์ของโซมาติกที่คล้ายกันภายในกลุ่ม ดังนั้นเราจึงตั้งสมมติฐานว่าการระบุ neoantigens ที่มีร่วมกันในมะเร็งเต้านมที่เกี่ยวข้องกับยีน *BRCA1* อาจใช้เป็นเป้าหมายสำหรับผลิตวัคซีน neoantigens การศึกษานี้รวบรวมข้อมูลจีโนมของตัวอย่างมะเร็งเต้านมที่มีหรือไม่มีการกลายพันธุ์ของยีน *BRCA1* แบบโซมาติกจากฐานข้อมูลมะเร็ง 3 แห่ง; Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC) และ Catalog of Somatic Mutations in Cancer (COSMIC) เราพบว่าการเปลี่ยนแปลงของเบสตำแหน่งเดียวที่พบมากที่สุดคือ C>T ทั้งในทั้งกลุ่ม *BRCA1*-positive และ -negative ยีนที่กลายพันธุ์บ่อยที่สุดคือ TP53 และ TTN ในตัวอย่าง *BRCA1*-positive และ PIK3CA และ TP53 ในตัวอย่าง *BRCA1*-negative จำนวนการกลายพันธุ์ทั้งหมดในตัวอย่างชนิดตำแหน่งเดียว และชนิดที่มีการแทรกหรือหายไปของเบสในกลุ่มตัวอย่าง *BRCA1*-positive สูงกว่าในตัวอย่าง *BRCA1*-negative สำหรับ neoantigens ที่มีร่วมกัน เราพบว่า *PIK3CA* H1047R, E545K, E542K และ N345K เกิดขึ้นซ้ำๆ ในกลุ่ม BRCA1-negative ในทุกฐานข้อมูล ในขณะที่กลุ่ม BRCA1-positive ยังไม่สามารถสรุปได้ การศึกษานี้ยังวิเคราะห์ตัวอย่างที่มีการกลายพันธุ์ BRCA1 ชนิดเจิร์มไลน์ที่ และพบว่า *TP53* R175H เป็นการกลายพันธุ์ที่พบบ่อยที่สุด แต่ไม่พบในการกลายพันธุ์นี้ในกลุ่ม BRCA1 ชนิดโซมาติก นอกจากนี้ neoantigens ที่พบบ่อยในตัวอย่าง BRCA1-negative ไม่ถูกพบในตัวอย่าง *BRCA1*-positive หรือ *BRCA1* ชนิดเจิร์มไลน์ ผลการศึกษาสะท้อนแสดงให้เห็นถึงผลการกลายพันธุ์ที่แตกต่างกันระหว่างมะเร็งเต้านมที่มีการกลายพันธุ์ของยีน *BRCA1* แบบโซมาติกและเจิร์มไลน์ และควรได้รับการศึกษาเพิ่มเติมต่อไป

สาขาวิชา	วิทยาศาสตร์การแพทย์	ลายมือชื่อนิสิต .....
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Lucksica Ruangapirom : Identification of shared neoantigens in BRCA1-related breast cancer. Advisor: Prof. APIWAT MUTIRANGURA, Ph.D. Co-advisor: CHATCHANAN DOUNGKAMCHAN, Ph.D.

Personalized neoantigen-based cancer vaccine has been shown to be safe and immunogenic in cancer patients; however, the manufacturing process can be costly and brings about delay in treatment. Using off-the-shelf cancer vaccine by targeting shared neoantigen may circumvent these problems. We identified *BRCA1*-mutated breast cancer as a candidate for shared neoantigens because of its clinical aggressiveness and its genotypic and phenotypic similarities suggesting common somatic mutational events within the group. Therefore, we hypothesized that shared-neoantigen may be identified among *BRCA1*-related breast cancer and may be used as targets for shared neoantigen vaccine. For analyses, we obtained genome sequencing data of breast cancer samples with or without somatic *BRCA1* mutations (BRCA1-positive and BRCA1-negative, respectively) from the 3 public cancer databases; The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC), and Catalogue of Somatic Mutations in Cancer (COSMIC). We found that SNVs were the dominant mutation type with C>T being the most abundant SNV type found in both *BRCA1*-positive and -negative groups. The most frequently mutated genes were *TP53* and *TTN* in *BRCA1*-positive and *PIK3CA* and *TP53* in *BRCA1*-negative samples. Total variant counts, the number of SNVs and indels were higher in *BRCA1*-positive than -negative group. As for shared neoantigens, we found *PIK3CA H1047R, E545K, E542K* and *N345K* recurrently in *BRCA1*-negative groups across all databases, whereas *BRCA1*-positive groups were inconclusive. We analyzed samples with known germline *BRCA1* mutations for shared neoantigens and found that *TP53 R175H* was the most frequent mutation but was not found among top somatic mutations in *BRCA1*-positive or -negative samples. Most of the top neoantigens identified in *BRCA1*-negative samples were not found in *BRCA1*-positive or germline *BRCA1* samples. Our findings reflected different mutational consequences between somatic and germline *BRCA1* breast cancers and should be further investigated.

Field of Study:	Medical Sciences	Student's Signature .....
Academic Year:	2021	Advisor's Signature .....
		Co-advisor's Signature .....

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HR	Homologous recombination
MHC	Major histocompatibility complex
NHEJ	Non-homologous end joining
PARPi	Poly-(adenosine diphosphate-ribose) polymerase inhibitors
SNV	Single nucleotide variation
SNVs	Single nucleotide variations
TAAs	Tumor-associated antigens
TNBC	Triple negative breast cancer
WGS	Whole genome sequencing
WES	Whole exome sequencing

CHAPTER I

INTRODUCTION

1. Background and Rationale

Cancer vaccine is an approach to cancer immunotherapies that involves activation of T cells against tumor antigens and can be use as therapeutic or preventive measures for cancer treatment [1]. Antigen targets for cancer vaccines are 1) over-expressed self-antigens known as tumor-associated antigens (TAAs), 2) cancer-testis antigens which are exclusively expressed in reproductive tissues, and 3) neoantigens which are exclusively expressed in tumor [2, 3]. Therefore, the ideal target for cancer vaccine is neoantigens because their absence in normal tissue mitigates the chance of autoimmune attack [4]. The process of manufacturing neoantigen-based cancer vaccine begins with identification of somatic mutations by comparing tumor genome to normal tissues within the same individuals. Somatic mutations that are found uniquely in tumor are then assessed for antigenicity by computerized algorithms and are validated *in vitro/in vivo* before being administered to patients [5-7]. Although personalized cancer vaccine approach has been shown to elicit immune responses in variety of cancers, complex manufacturing process that is also completely individualized results in cost and delay in availability of treatment which prevents access to such treatment for all patients [8]. To overcome this problem, off-the-shelf cancer vaccine targeting neoantigens that are "common" or "shared" among the group of cancer patients may help reduce cost and time of access to cancer vaccine. In this study, we aimed to identify shared (or common or public) neoantigens found recurrently in *BRCA1*-related breast cancer patients that may be used as target neoantigen for shared vaccine development.

The reasons we chose to identify shared neoantigens in *BRCA1*-related breast cancers is not only because breast cancer is the first leading cause of death by cancer among women [9] and 10% among which are *BRCA1*-related [10, 11], but also *BRCA1*-mutated breast cancer shares characteristic mutational signatures suggesting a non-random mutational event within the group [12, 13]. Additionally, *BRCA1*-mutated breast cancer also shares phenotypic similarities such as morphology, molecular subtypes and responsiveness to poly-(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) treatment. To illustrate further, studies found approximately 70% of *BRCA1*-mutated breast cancer to exhibit basal-like in molecular subtype compared to 20% in BRCA1-wild type breast cancer [14], 57-68% of *BRCA1*-mutated breast cancer exhibit triple negative breast cancer (TNBC) in surrogate subtype compared to 13% in *BRCA1*-wild type breast cancer [15, 16], and 50-79% response to PARPi compared to 10-33% in *BRCA1*-wild type cases [17, 18]. Because of these similarities within *BRCA1*-mutated breast cancer, we hypothesized that some neoantigens may be found recurrently across individuals with *BRCA1* mutations and may be used as the neoantigens for off-the-shelf cancer vaccine, both for therapeutic purposes for cases with somatic BRCA1 mutations, and for prevention purposes for those with germline BRCA1 mutations.

The concept of shared-antigen cancer vaccines has been around for a decade. However, antigen targets for shared antigen cancer vaccine are mostly TAAs [19]. This is because neoantigens are less abundant than TAAs

and are highly-individualized; however, recent studies have shown successful treatment using neoantigen-based shared cancer vaccine in some cancers such as *IDH1* R132H for glioblastoma [4, 20], *KRAS* G12D for colon cancer [21]. Other common neoantigens that have been identified and has been proposed as targets for cancer vaccines are such as *TP53* R175H and *PIK3CA* H1047R for gastric cancer [22] and *RET* M198T for thyroid cancer [23, 24]. Nevertheless, shared target neoantigens for *BRCA1* breast cancer nowadays are such as *HER2* and *MUC1* which are still targeting TAAs [25-28], neoantigen-based shared vaccine for *BRCA1*-related breast cancers are not reported to our knowledge.

In this study, we proposed potential neoantigen targets that are found commonly in *BRCA1*-positive, -negative and germline *BRCA1*-mutated samples that may be used for vaccine development. We included samples from large open-access public cancer genome databases; TCGA, ICGC and COSMIC to identify top recurrent mutations from which we also predicted antigenicity of proteins with top recurrent mutations. We also analyzed mutation landscapes and top recurrent mutated genes of *BRCA1*-positive and -negative breast cancer to provide some insights into biological differences that occur between these 3 *BRCA1*-related breast cancer groups.

2. Review literature

Personalized neoantigen-based cancer vaccine

The personalized neoantigen-based vaccine is one of the immunotherapies which utilize highly specific tumor neoantigen to expand specific T-cells against the tumor while lessening autoimmune toxicity [29, 30]. (Figure 1) Cancer cells have genetic alterations which could be unique when compared to normal tissue counterpart. When the non-synonymous mutations occur, the mutant proteins are generated [31].The mutant proteins unique to cancerous tissues, which are recognizable by the HLA class I/II molecules and consequently induce CD4 and CD8 T-cell responses, are known as 'neoantigens' [32-34]. (Figure 2)

The application of the neoantigen-based cancer vaccine has originally been focused on personalized treatment. Nevertheless, the goal of our study is to apply the principle of cancer vaccine for cancer prevention. The rationales to support this application include 1) targeting neoantigens before the tumor mass forms surpasses inhibitory tumor immunosuppressive environment that often compromises the outcome of neoantigen-based cancer treatment.[35-39] (Figure 3); 2) cancer vaccine targeting viral cancer such as hepatitis B (HBV) and human papillomavirus (HPV) shows remarkable results only when used as prevention, not as treatment [40-42]. These support our hypothesis that neoantigen-based cancer vaccine may be used as prevention for non-viral cancer [35].

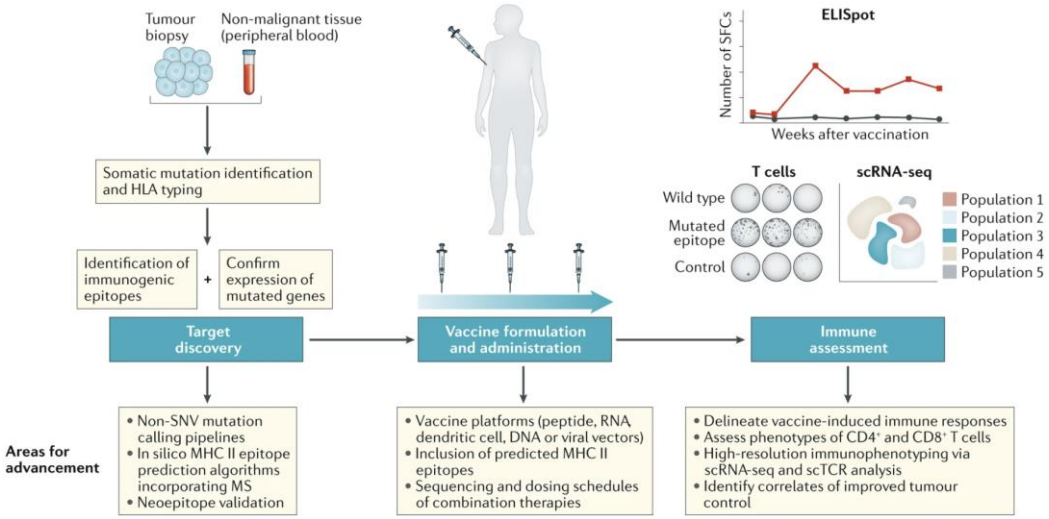


Figure 1 Algorithm-based identification of neoantigens for use in therapeutic vaccines [35]

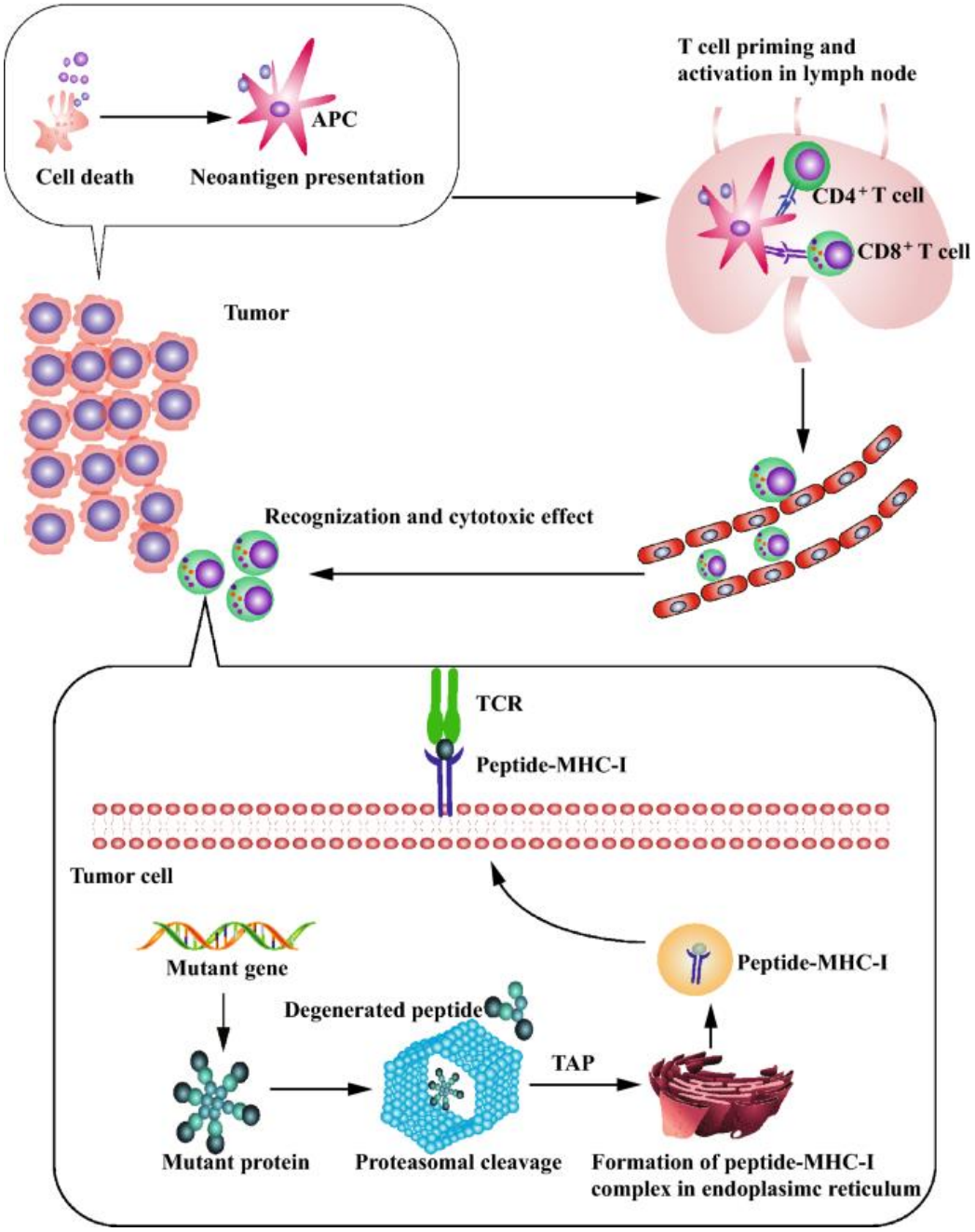


Figure 2 Cancer-immunity cycle and neoantigen presentation [34]

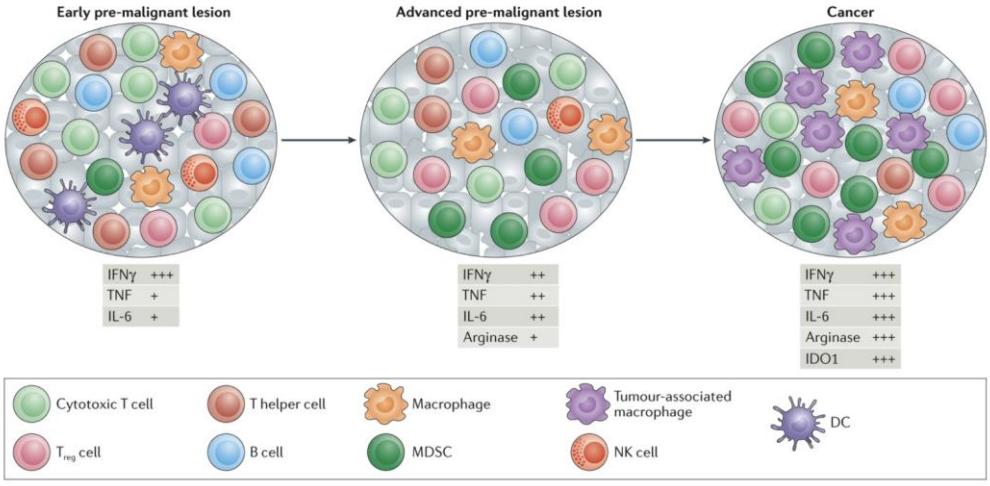


Figure 3 Progressive stages of cancer development are accompanied by changes in the local immune microenvironment [35]

Using neoantigens as targets in non-viral cancer preventive vaccine

There are several potential targets for preventive cancer vaccines. Traditional targets that have been successfully preventing cancer are viral protein for viral cancer such as hepatitis B virus (HBV), human papillomavirus (HPV) which are widely used in vaccination programs of many countries [43, 44]. However, it is more challenging in non-viral cancer. Tumor-associated antigens (TAAs), which are non-mutated proteins abnormally expressed in tumors, have been used as targets for preventive cancer vaccines. However, TAAs are self-molecules and still expressed in normal tissues, autoimmunity and self-tolerance would take place[45]. Therefore, neoantigens, which are unique to an individual tumor and not found in normal tissues, are the reasonable targets to activate immunity against cancer while preventing autoimmunity [46].

Pre-malignant lesion as an initial target

The aim of using cancer vaccine as preventive measure is to target cancer before suppressive tumor microenvironment emerges. Therefore, the ideal situation would be to target neoantigens that arose in premalignant lesions. Cancer development starts from early pre-malignant lesions, advanced pre-malignant lesions and to fully developed cancer. In patients with no existing immunity to premalignant lesions will finally progress to fully developed cancer. Preventive cancer vaccine targeting premalignant lesion, when given to the patients, will result in equilibrium (a tie between cancer and immune system) or elimination of premalignant lesion (immune system overcoming cancer progression) [35]. (Figure 4) The best way to prevent the progression of the pre-malignant lesion is to formulate a vaccine from the pre-malignant lesion and administer the vaccine before cancer occurs. Nevertheless, this approach may only be applicable in cancer where premalignant lesions are easily detected which is not breast cancer.

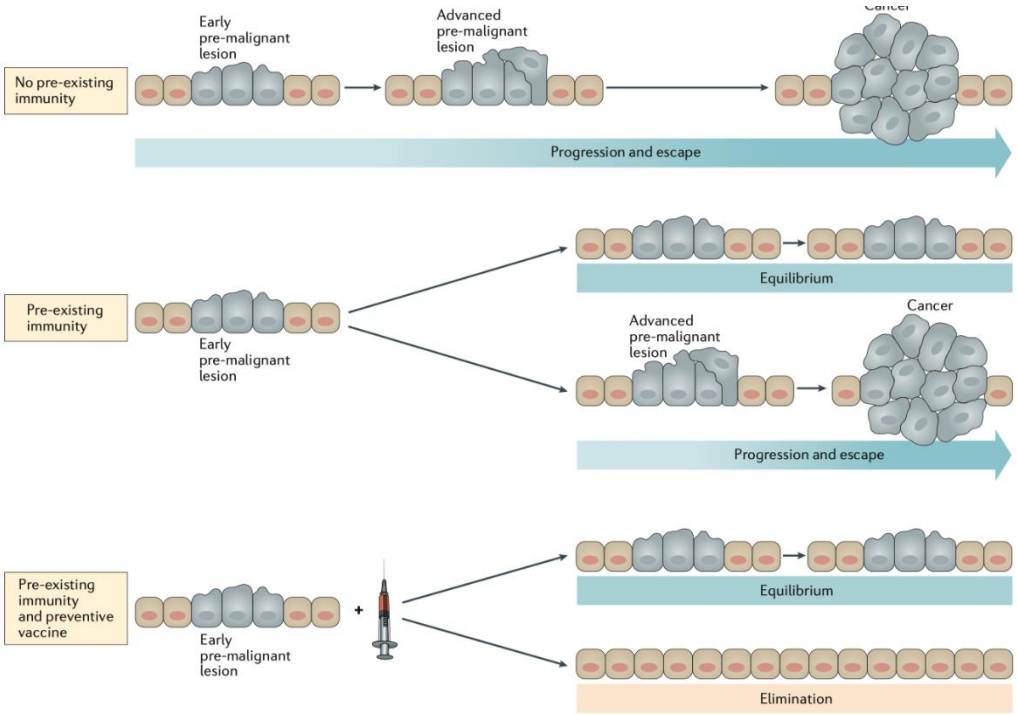


Figure 4 Boosting immune system with preventive cancer vaccine determines disease outcomes [35]

Neoantigens identified in fully-developed cancer will be used as targets because of mutation similarity between premalignant and cancerous lesions

Targeting premalignant neoantigens is still not feasible in many cancers especially the ones with decreased sensitivity of cancer screening approach. Breast cancer is among those cancer where premalignant lesions/tumors are not easy to acquire. To circumvent this problem, we utilized the multistep process of carcinogenesis where fully developed cancer may provide a list of neoantigen history from premalignant to cancerous lesions. This mutational history is found as mutational signatures - the imprint of the results of all exogenous and endogenous DNA damaging events. The final mutation portrait is the sum of all the different mutational processes (A-D) in the lifetime (Figure 5) [47]. Lesion progression starts from the premalignant lesion, developing cancer to fully developed cancer, and some degree of mutational similarities retain over cancer evolutionary. Next-generation sequencing (NGS) from advanced cancer also reveals all patterns of mutation signatures from primary cancer (Figure 6) [48]

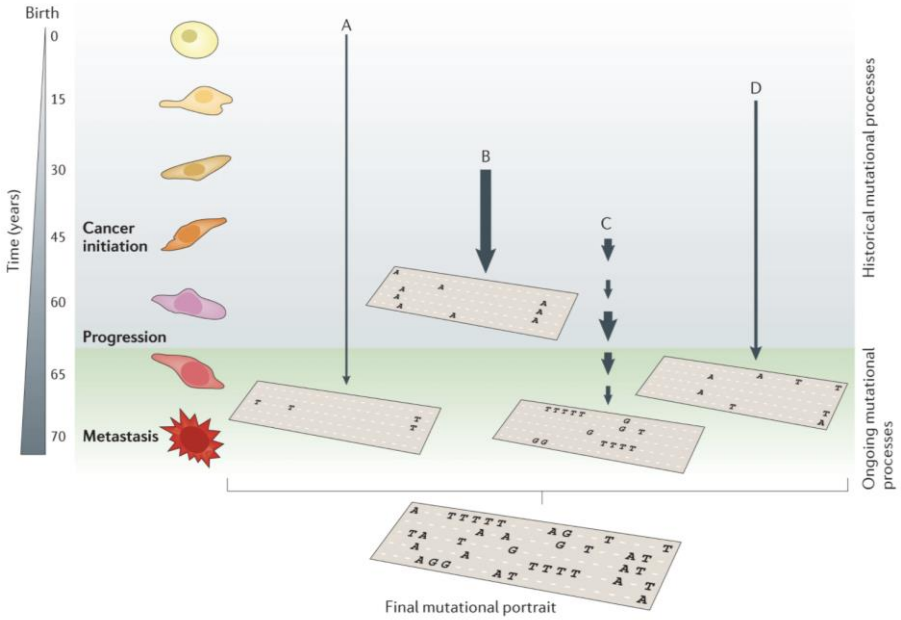


Figure 5 Mutational processes over the course of cancer development [47]

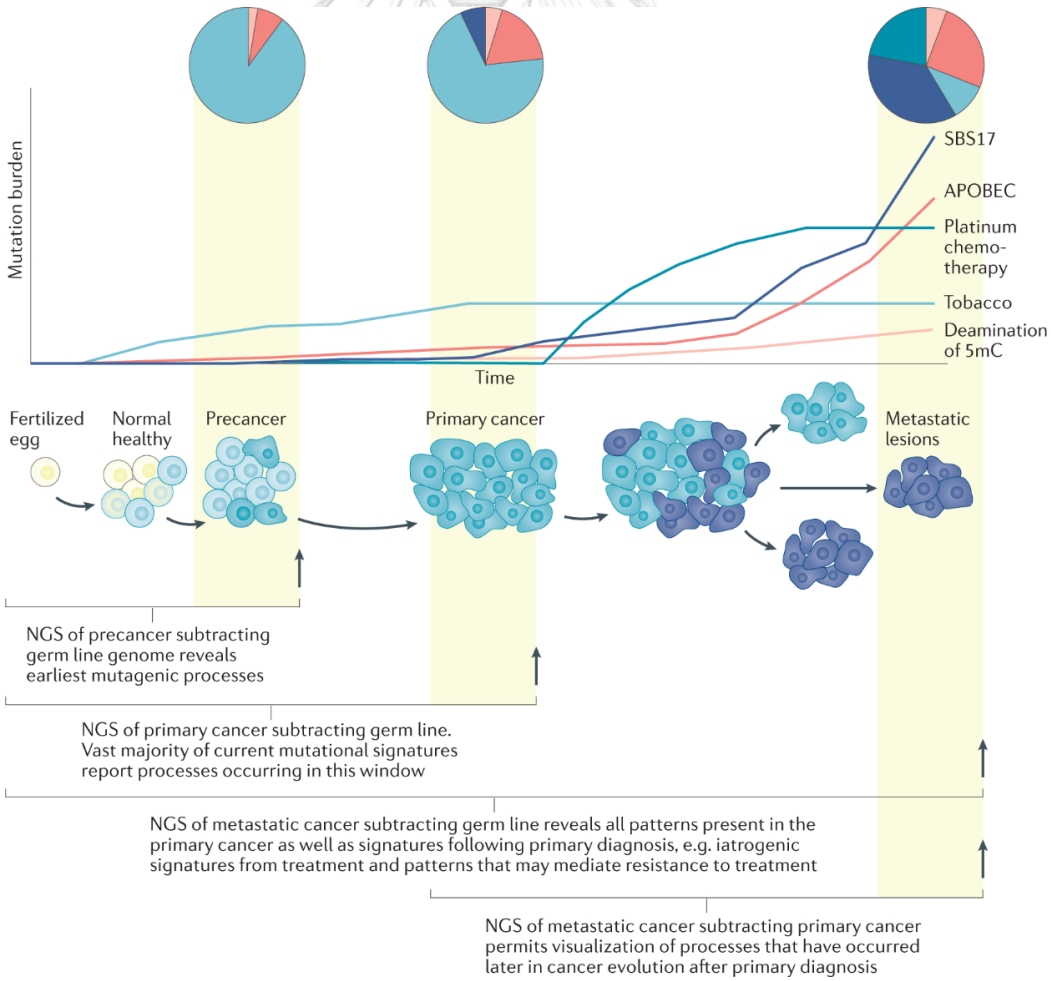


Figure 6 Dynamics of mutational signatures over cancer evolutionary [48]

Therefore, our experiment is to use the data of whole genome, whole exome sequencing and target genome sequencing for the identification of neoantigen in fully-developed cancer. We propose to use the neoantigens found recurrently in fully-developed cancer tissues to provide generalized neoantigen coverage against emerging cancer among the target population, in which case is *BRCA1* carriers.

Importance of *BRCA1* mutation

In 2020, Breast cancer is the first leading cause of global cancer incidence, with 2.3 million cases, and cancer mortality, 0.68 million deaths, in women worldwide [49]. *BRCA1*-mutation accounts for 2% of all breast cancer.[11, 50] Moreover, *BRCA1*-mutated carriers have high accumulative risks to develop cancer and the risks increase with age. The accumulative risks are 43% by age 50 years, 56% by age 60 years, 66% by age 70 years, and 72% by age 80 years [51]. *BRCA1*-mutated carriers seem to unavoidably develop cancer unless any preventive action is taken.

The explanation of BRCA1 dysfunction and cancer development is that BRCA1 plays a major role in double strand break (DSB) DNA repair. There are two major DSB repair pathways (Figure 7) [52]. First is homologous recombination (HR) that uses double strand DNA as a template and known as 'error-free repair'. The second is non-homologous end joining (NHEJ) which the break ends are directly ligated without the homologous template [53, 54]. *BRCA1* is the major facilitator in the error-free HR repair pathway.

BRCA1 promotes HR in two main steps, the break end resection[55, 56] and loading key protein of HR named RAD51 [57, 58]. (Figure 8)[52] This explains that *BRCA1* is important in error-free DNA repair and explain why the loss of *BRCA1* function produces a vast number of mutations.

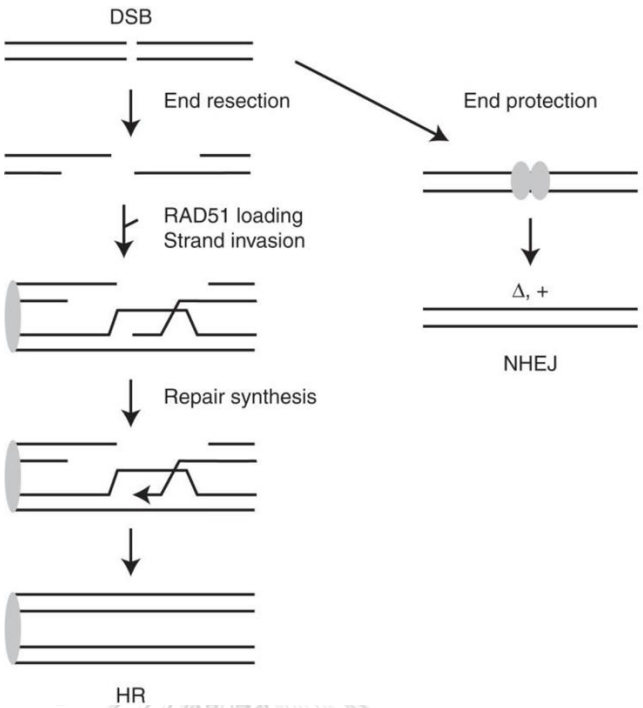


Figure 7 Schemes of double-strand break (DSB) repair by homologous recombination (HR) and non-homologous end joining (NHEJ) [52]

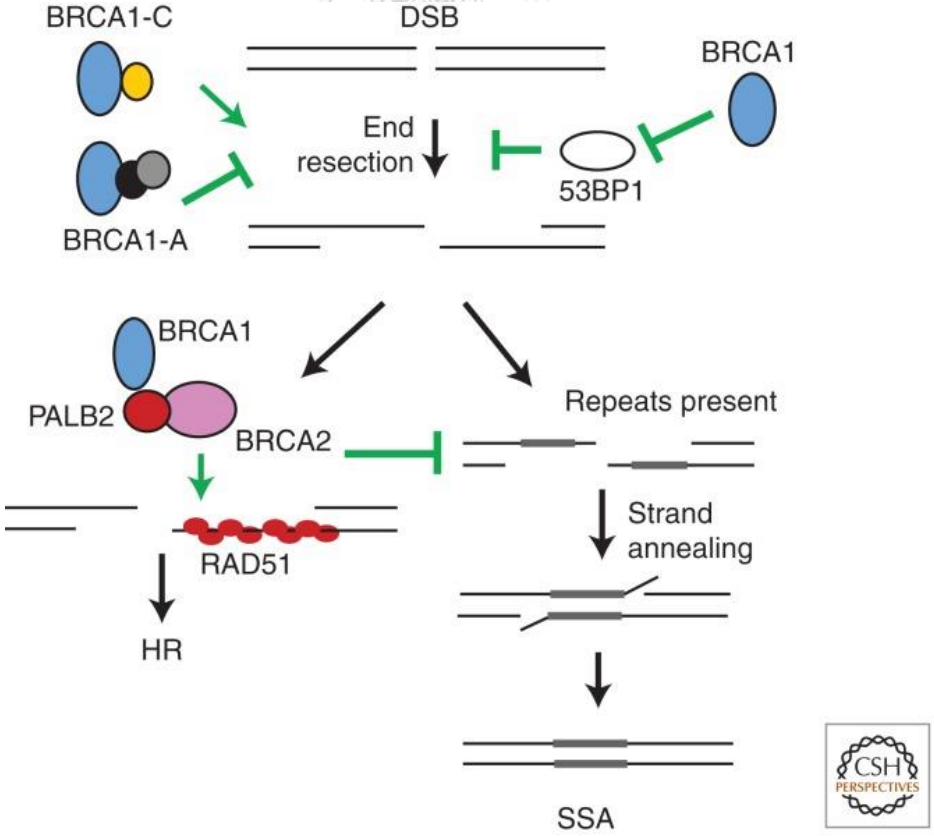


Figure 8 *BRCA1* roles in homologous recombination (HR) [52]

Mutational similarities among *BRCA1*-mutated breast cancer samples

Because our study aims to identify neoantigens in *BRCA1*-mutated breast cancer samples for the use as a generalized preventive cancer vaccine, it is important that those mutations are found recurrently among the samples. Although, cancer neoantigens are known to be highly individualized suggesting low recurrent rate across individuals, previous studies showed that *BRCA1*-mutated breast cancer have similar mutational signatures and is strongly associated with base substitution signature 3 [59]. Additionally, *BRCA1*-mutated breast tumors exhibit similar phenotypes. For example, previous studies found that 74% of *BRCA1*-mutated breast cancer exhibit basal-like[14] in molecular subtype and 68% of BRCA1-mutated breast cancer exhibit triple-negative breast cancer (TNBC) [60] in surrogate subtype which reflect the similar mutational process. Taken together, these evidences may suggest higher chance of finding recurrent mutations among breast cancer samples with *BRCA1* mutations compared to sporadic breast cancer samples.

The approach to identifying neoantigens for individualized neoantigen-based therapeutic cancer vaccine will be used in to identify candidate neoantigens in this study.

Individualized neoantigen-based therapeutic cancer vaccine approach has paved a reliable path to identifying candidate neoantigens and the protocol for neoantigen identification is well-established. The process starts from sequencing tumors and normal tissue by next-generation sequencing technologies. Somatic mutations found uniquely in tumors will be included for the next analysis step which is antigenicity prediction [5-7]. There are several algorithms used for this process such as netMHC or netMHCpan. These algorithms were trained to predict the binding affinities between MHC class I or II alleles and possible antigenic peptides of 8-12 amino acids in length [61]. Therefore, in our approach to developing neoantigen-based preventive cancer vaccines, we will adopt this approach of step-wise cancer-unique somatic mutations followed by antigenicity prediction to generate our candidate neoantigens for preventive cancer vaccine development.

Previous studies on preventive cancer vaccine effort

In the early efforts to develop preventive cancer vaccine, most clinical trials utilized TAAs in preventive cancer vaccine settings. Sharma et al (2012) studied the effect of the *HER2*-based vaccine in patients with ductal carcinoma in situ (DCIS), precancerous lesion of breast cancer [25]. The results showed that 5 of 27 (18.5%) patients who got vaccinated before resection surgery have no residual lesions at the time of surgery and the other 22 patients with residual lesions demonstrated decreasing in *HER2* expression. Common adverse events are malaise (72.4%), injection site soreness (58.6%), fever (27.5%) and headache (24%).[25] The other TAA that is used in a preventive setting is *MUC1*. Kimura et al (2013) tested the effect of the *MUC1*-based vaccine in patients without cancer who had a history of premalignant lesions (colonic adenoma). The results showed that 17 of 39 (43.6%) vaccinated patients had a high level of anti-*MUC1* IgG and long-lasting immune memory. The other 22 patients showed a lack of response that was associated with high levels of pre-vaccination circulating myeloid-derived suppressor cells. Adverse events are erythema (87.5%), injection site soreness (80%) and flu-like symptoms (37.5%).[62] Both studies showed good clinical outcomes. There were adverse events though these toxicities were acceptable.

Chao C. et al (2020) had similar idea with our study and aimed to identify recurrent neoantigens in colorectal cancer as potential immunotherapy targets [21]. They collected whole exome sequencing data from multiple cohort (e.g. TCGA) and analyzed somatic mutation landscape. The study showed high-frequency mutations, e.g., *KRAS* G12D (8%), *KRAS* G12D (5.8%), *PIK3CA* E545K (3.5%), which can be recognized by many common HLA molecules in Chinese and TCGA cohort. It implied that these mutations have a potential to be public neoantigens for colorectal cancer immunotherapy targets [21]. There are also ongoing trials that are studying the effect of neoantigen-based preventive vaccines, but it does not mention about the approach of neoantigen identification and candidate selection. There are two phase I/II trials that are interested in colorectal cancer. The study (NCT05078866) aims to evaluate the effect of Nous-209 vaccine, which is a neoantigen-based vaccine, in Lynch syndrome patients who have no evidence of active cancer [63]. Another study (NCT01885702) aims to evaluate the toxicity of vaccination with frameshift-derived neoantigen-loaded dendritic cells (DC) of colorectal cancer patients with an MSI-positive colorectal cancer and persons who are known to be carriers of a germline MMR-gene [64]. Both studies aim to evaluate safety and effect of neoantigen-based vaccine in terms of prevention. But there are no trial that studied in *BRCA1*-mutated cancer. So, our study will provide the candidate neoantigen lists that benefit neoantigen-based vaccine in *BRCA1*-mutated patients.

3. Research objectives

1. To Identify recurrent somatic mutations of *BRCA1*-postive and -negative breast cancer
2. To Identify candidate neoantigen targets for preventive cancer vaccine development

4. Research question

Primary research question

- Are there any recurrent somatic mutations among *BRCA1*-related breast cancer?

Secondary research question

- Do recurrent somatic mutations of *BRCA1*-related breast cancer have the potential to be candidate neoantigen targets for neoantigen-based cancer vaccine?
- What are the *BRCA1*-related breast cancer mutational profiles?

5. Hypothesis

Somatic mutations in *BRCA1*-related breast cancer may have recurrent mutations sufficient to develop a generalized preventive neoantigen cancer vaccine.

6. Keywords

Cancer vaccine

Somatic *BRCA1*

Germline *BRCA1*

Breast cancer

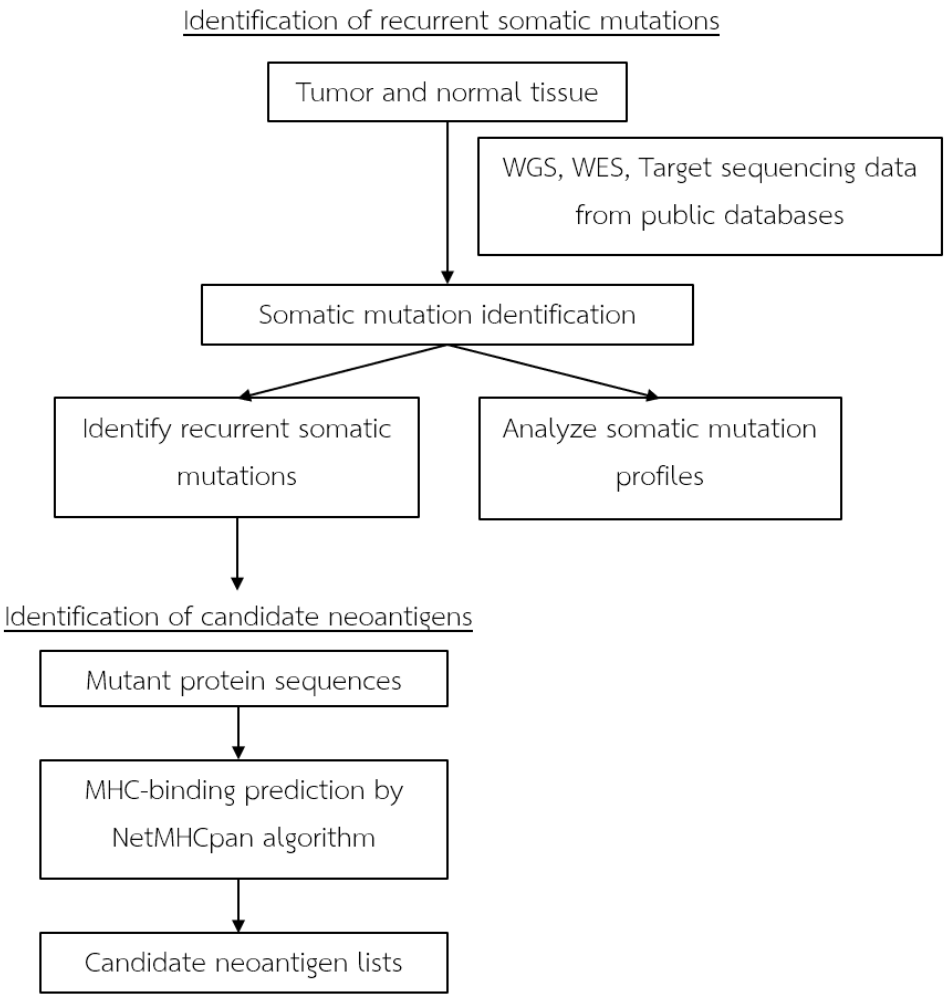
Immunotherapy

Shared neoantigen

7. Study design

Descriptive study

8. Conceptual framework



CHAPTER II

RESEARCH METHODOLOGY

1. Target Population

BRCA1-related breast cancer patients

2. Approach to participants

We collect genomic data from 3 cancer genome databases: International Cancer Genome Consortium (ICGC), The Cancer Genome Atlas (TCGA) and Catalogue of Somatic Mutations in Cancer (COSMIC) for sequencing data of breast cancer samples with and without *BRCA1*-mutation.

3. Inclusion and exclusion criteria

Inclusion criteria

- Primary breast cancer samples

Exclusion criteria

- Samples with single gene target sequencing
- Samples with known germline *BRCA1* mutations reported by previous studies [12, 65, 66] (Supplementary table 4).

4. Sample identification

Samples with "pathogenic" or "likely pathogenic" somatic *BRCA1* mutations, which were classified by ACMG guidelines 2015, and met the criteria will be referred to in this paper as "*BRCA1*-positive". Samples which were known to have wild-type *BRCA1* sequence were classified as "*BRCA1*-negative".

The American College of Medical Genetics and Genomics (ACMG) guidelines 2015

ACMG guidelines [67] are international-accepted standards and guidelines for interpretation of sequence variants. The classification criteria based on types of variant evidence. (e.g. population data, computational data, functional data, segregation data, etc.) (Table 1) There are 28 criteria which were divided into 16 pathogenic criteria and 12 benign criteria. Variants are classified into 5 types: Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign. (Table 2) In this study, we accessed ACMG interpretation results via "VarSome The Human Genomics Community" (https://varsome.com)

Table 1 Criteria by evidence type [67]

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Table 2 Rules for Combining Criteria to Classify Sequence Variants [67]

Pathogenic

1. 1 Very Strong (PVS1) AND
    1. ≥1 Strong (PS1–PS4) OR
    2. ≥2 Moderate (PM1–PM6) OR
    3. 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) OR
    4. ≥2 Supporting (PP1–PP5)
2. ≥2 Strong (PS1–PS4) OR
3. 1 Strong (PS1–PS4) AND
    1. ≥3 Moderate (PM1–PM6) OR
    2. 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR
    3. 1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5)

Likely Pathogenic

1. 1 Very Strong (PVS1) AND 1 Moderate (PM1–PM6) OR
2. 1 Strong (PS1–PS4) AND 1–2 Moderate (PM1–PM6) OR
3. 1 Strong (PS1–PS4) AND ≥2 Supporting (PP1–PP5) OR
4. ≥3 Moderate (PM1–PM6) OR
5. 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR
6. 1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5)

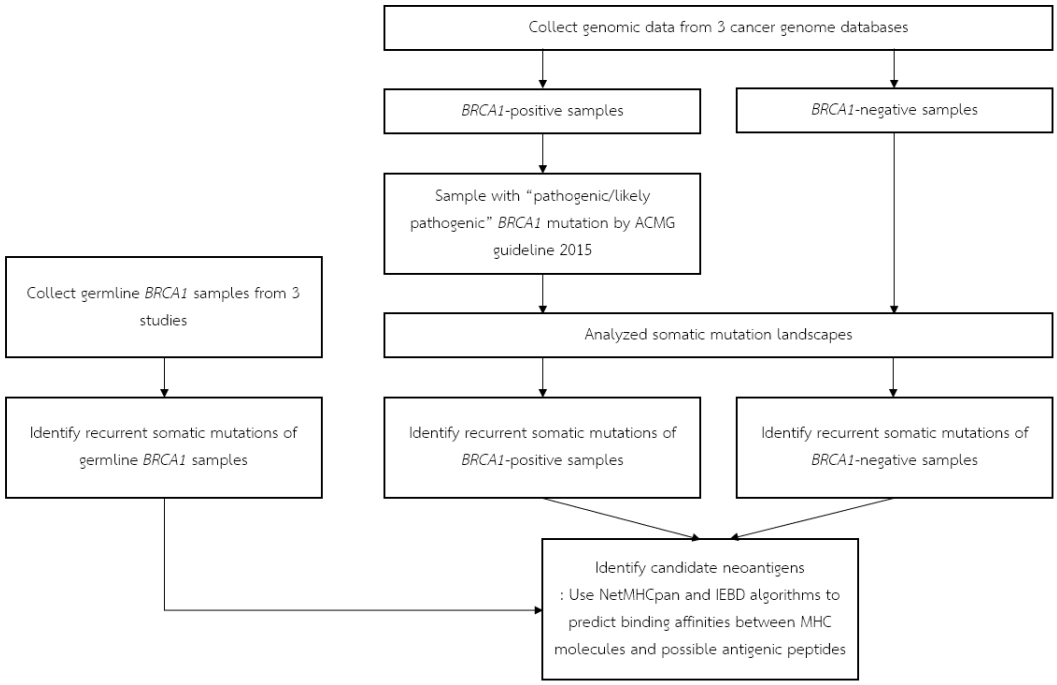
Benign

1. 1 Stand-Alone (BA1) OR
2. ≥2 Strong (BS1–BS4)

Likely Benign

1. 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) OR
2. ≥2 Supporting (BP1–BP7)

5. Experimental procedure



5.1 Collect genomic data of breast cancers with and without BRCA1 mutation from 3 cancer genome databases

5.1.1 The Cancer Genome Atlas (TCGA)

: https://dcc.icgc.org/

5.1.2 International Cancer Genome Consortium (ICGC)

: https://portal.gdc.cancer.gov/

5.1.3 Catalogue of Somatic Mutations in Cancer (COSMIC)

: https://cancer.sanger.ac.uk/cosmic

5.2 Search term

5.2.1 For TCGA and ICGC databases, the search term "primary site is breast and gene is *BRCA1*" were used to locate samples with sequencing data on *BRCA1* gene.

5.2.2 For COSMIC database (data version: May 28,2021), the search term "gene: *BRCA1*, tissue: breast" were used.

5.3 Select samples that met the inclusion and exclusion criteria

5.3.1 Inclusion criteria

- Primary breast cancer samples

5.3.2 Exclusion criteria

- Samples with single gene target sequencing
- Samples with known germline *BRCA1* mutations reported by previous studies [12, 65, 66] (Supplementary table 4)

5.4 Samples with "pathogenic" or "likely pathogenic" somatic *BRCA1* mutations which classified by 2015 American College of Medical Genetics and Genomics (ACMG) criteria will be referred to in this paper as "*BRCA1*-positive". Samples which were known to have wild-type *BRCA1* sequence were classified as "*BRCA1*-negative".

5.5 Analyze somatic mutation landscapes

5.5.1 Variant types

5.5.2 Single nucleotide variants classification

5.5.3 Variant classification

5.5.4 Variant counts per sample

5.6 Frequently mutated genes in *BRCA1*-positive and -negative breast cancer samples

5.7 Identify recurrent somatic mutations and cumulative coverage of each database

5.8 To compare recurrent mutations between BRCA1-positive/-negative samples and germline BRCA1-mutatated samples, we identify recurrent somatic mutations from 3 studies that reported next-generation sequencing data on samples confirmed to be germline *BRCA1* mutations.

5.9 Predicted antigenicity of top recurrent somatic mutations

5.9.1 Assess binding affinities between mutated epitopes with Major Histocompatibility Complex (MHC) class I by netMHCpan [68, 69] and The Immune Epitope Database (IEDB) algorithms [70]. We used 2

prediction methods, NetMHCpan BA 4.1 and NetMHCpan EL4.1 [61, 71]. We used 145 MHC class I alleles in this study to cover 99% of all MHC class I in world-wide population [72].

5.9.1.1 Criteria of possible neoantigens

- MHC Class I/peptide pairs with stronger than moderate binding affinity (IC50<500) will be determined as possibly antigenic [73].

- Antigenic epitopes are generated exclusively from mutated protein and cannot be found in wild-type protein.

5.9.2 Assess binding affinities between mutated epitopes with Major Histocompatibility Complex (MHC) class II by the Immune Epitope Database (IEDB) algorithms [70] which are the concensus 2.22 approach [74] including NN-align 2.3 [75], SMM-align [76], CombLib [77] and Sturniolo [78]. If none of these methods are available for the allele, NetMHCIIpan 4.0 [61] is used. We used 27 MHC class II alleles in this study to cover 99% of all MHC class II in world-wide population [79]. We selected 12-mer to 18-mer peptides [80, 81].

5.9.2.1 Criteria of possible neoantigens

- Consensus percentile rank of the top 10%. Alternatively, selecting peptides binding with MHC Class II at less than 1,000 nM were classified into binder [82, 83].

- Antigenic epitopes are generated exclusively from mutated protein and cannot be found in wild-type protein.

5.10 List candidate neoantigens

6. Statistical analysis

Mann-Whitney U test to compare variant counts between *BRCA1*-positive and -negative samples within the same databases was performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

$P < 0.05$ was considered statistically significant.

7. Ethical Consideration

All data used in this study are from available public databases with original study's informed consent. This study doesn't require additional informed consent.

8. Expected or anticipated benefit gain

This study will explain more mutation profiles and characteristics of *BRCA1*-related breast cancer. And this study will prove if there are any recurrent somatic mutations that have a potential to be candidate neoantigen targets for preventive cancer vaccine development. Preventive cancer vaccine will eliminate the tumor before it forms and reduce burden of the disease for patients as well as the burden of government healthcare cost on cancer treatment.

9. Challenges

- Each database has different variant calling pipelines so we will analyze somatic mutation each database separately.

- We do not know if recurrent somatic mutations in sporadic breast cancer are different form recurrent somatic mutations in BRCA1-mutated patients. We should identify recurrent somatic mutation in sporadic breast cancer in further study.

CHAPTER III

RESULTS

1. Characteristics of *BRCA1*-positive and *BRCA1*-negative samples

The characteristics of the breast cancer samples with pathogenic or likely pathogenic *BRCA1* mutation (referred to as *BRCA1*-positive) were shown in table 3. With inclusion and exclusion criteria, we were able to include into our study 12, 15 and 66 samples from TCGA, ICGC and COSMIC databases, respectively. All sample IDs included in this study can be found in Supplementary table 5. Mean age of sample in TCGA, ICGC and COSMIC were 59.58 (±12.861), 58.73 (±16.26) and 54.14 (±14.91) years, respectively, excluding 38 samples with unknown age from COSMIC. All samples were from female donors except for 1 male donor from COSMIC. Most samples were stage-2 breast cancer in TCGA (8/12; 66.67%) and ICGC (9/15; 60.00%), but unknown stage was the majority in COSMIC (52/66; 78.78%). For histology, the majority of samples were reported as infiltrating ductal carcinoma in TCGA (11/12; 91.67%) and ICGC (14/15; 93.33%); and unknown histology (42/66; 63.63%) followed by infiltrating ductal carcinoma (20/66 30.30%) in COSMIC. For molecular subtype, 29/66 (43.94%) of COSMIC samples were hormonal-receptor positive, whereas most samples from TCGA and ICGC showed unidentified molecular subtype. For sequencing data type, all samples in TCGA were whole exome sequencing (WES) (12/12; 100%). Samples in ICGC were reported in WES (8/15; 53.33%) and Whole genome sequencing (WGS) (7/15; 46.67%). Samples in COSMIC are consist of WES (9/66; 13.64%), WGS 11/66; 16.67%) and targeted sequencing (46/66; 69.69%).

Table 3 Characteristic summary of *BRCA1*-positive samples

Characteristics	TCGA	ICGC	COSMIC
Sample size (n)	12	15	66
Age			
Mean	59.58 (±12.86)	58.73 (±16.26)	54.14 (±14.91)
Unknown	0	0	38
Sex			
Female	12 (100%)	15 (100%)	65 (98.48%)
Male	0	0	1 (1.52%)
The American Joint Committee on Cancer (AJCC) stage			
I	3 (25.00%)	1 (6.67%)	0

Characteristics	TCGA	ICGC	COSMIC
II	8 (66.67%)	9 (60.00%)	3 (4.55%)
III	0	5 (33.33%)	7 (10.61%)
IV	0	0	4 (6.06%)
Unknown	1 (8.33%)	0	52 (78.78%)
Histology type (count/%)			
Infiltrating ductal carcinoma, NOS	11 (91.67%)	14 (93.33%)	20 (30.30%)
Lobular carcinoma, NOS	0	0	3 (4.55%)
Metaplastic carcinoma, NOS	1 (8.33%)	1 (6.67%)	0
Acini cell carcinoma	0	0	1 (1.51%)
Phyllodes tumor	0	0	1 (1.51%)
Unknown	0	0	42 (63.63%)
Molecular subtype (count/%)			
ER-, HER2-	0	2 (13.33%)	5 (7.58%)
ER-, HER2+	0	2 (13.33%)	1 (1.51%)
ER+, HER2-	0	1 (6.67%)	3 (4.55%)
ER+, HER2+	0	0	0
Hormone receptor +	0	0	29 (43.94%)
Hormone receptor -	0	0	0
Unknown	12 (100%)	10 (66.67%)	28 (42.42%)
Sequencing data type			
WGS	0	7 (46.67%)	11 (16.67%)
WES	12 (100%)	8 (53.33%)	9 (13.64%)
Target sequencing	0	0	46 (69.69%)

BRCA1-negative samples identified by samples with no mutations at *BRCA1* gene were also included in our analysis for comparison. There were 123, 1,714 and 3,158 *BRCA1*-negative samples identified in TCGA, ICGC and COSMIC, respectively (Table 4). All sample IDs included in this study can be found in Supplementary table 5. Mean age of the samples in TCGA, ICGC and COSMIC were 58.34 (±13.68), 56.67 (±13.85) and 59.39 (±12.49) years, respectively, with 3 samples from TCGA, 116 samples from ICGC and 2,953 samples from COSMIC with unknown age. Female donors contributed to 119 samples (96.74 %) from TCGA, 1,699 (99.12%) from ICGC and 2,989 (94.65%) samples from COSMIC. For the stage at which samples were obtained, most samples in TCGA were from stage 2 (65/123; 52.84%) while most have unknown staging in ICGC (1,532/1,714; 89.38%) and COSMIC (2,244/3,158; 71.06%). For histology, infiltrating ductal carcinoma was the majority in TCGA (102/123; 82.92%). Most samples in ICGC (1,144/1,714; 66.74%) and COSMIC (1,491/3,158; 47.21%) had unknown histology, followed by infiltrating ductal carcinoma (485/1,714; 28.29%) in ICGC and (1,304/3,158; 41.29%) in COSMIC. For molecular subtype, information was not provided for most samples in all databases. However, ER-positive/HER2-negative and hormone receptor-positive was the majority subtype in ICGC (477/1,714; 27.82%) and COSMIC (1,132/3,158; 35.85%), respectively, if information was provided. For the sequencing data type, all samples in TCGA were whole exome sequencing (WES) (123/123; 100%). Samples in ICGC were reported in WES (1,035/1,714; 60/38%) and Whole genome sequencing (WGS) (679/1,714; 49.61%). Most samples in COSMIC were WES (9/3,158; 0.28%), WGS (70/3,158; 2.22%) and mostly targeted sequencing (3,079/3,158; 97.50%). This showed similar sample demographics between *BRCA1*-positive and *BRCA1*-negative samples within the same database. However, we analyzed each database separately because of variations in sequencing data type and variant calling protocols among databases [84].

Table 4 Characteristic summary of *BRCA1*-negative samples

Characteristics	**TCGA**	**ICGC**	**COSMIC**
Sample size	123	1,714	3,158
Age			
Mean	58.34 (±13.68)	56.67 (±13.85)	59.39 (±12.49)
Unknown	3	116	2,953
Sex			
Female	119 (96.74%)	1,699 (99.12%)	2,989 (94.65%)
Male	4 (3.25%)	15 (0.87%)	169 (5.35%)
The American Joint Committee on Cancer (AJCC) stage			
I	16 (13.00%)	51 (2.97%)	314 (9.94%)

Characteristics	TCGA	ICGC	COSMIC
II	65 (52.84%)	96 (5.60%)	257 (8.14%)
Characteristics	TCGA	ICGC	COSMIC
III	36 (29.26%)	31 (1.80%)	158 (5.00%)
IV	4 (3.25%)	4 (0.23%)	185 (5.86%)
Unknown	2 (1.62%)	1,532 (89.38%)	2,244 (71.06%)
Histology type (count/%)			
Infiltrating ductal carcinoma, NOS	102 (82.92%)	485 (28.29%)	1,304 (41.29%)
Lobular carcinoma, NOS	15 (12.19%)	36 (2.10%)	258 (8.17%)
Infiltrating ductal and lobular	2 (1.62%)	0	76 (2.41%)
Tubular carcinoma	0	6 (0.35%)	0
Metaplastic carcinoma, NOS	2 (1.62%)	4 (0.23%)	16 (0.51%)
Papillary carcinoma	1 (0.81%)	18 (1.05%)	0
Adenocarcinoma, NOS	0	6 (0.35%)	0
Mucinous carcinoma	1 (0.81%)	13 (0.75%)	0
Adenoid cystic carcinoma	0	1 (0.05%)	0
Acini cell carcinoma	0	0	13 (0.41%)
Carcinoma with neuroendocrine	0	1 (0.05%)	0
Unknown	0	1,144 (66.74%)	1,491 (47.21%)
Molecular subtype (count/%)			
ER-, HER2-	0	0	386 (12.22%)
ER-, HER2+	0	0	52 (1.65%)
ER+, HER2-	0	477 (27.82%)	0
ER+, HER2+	0	0	19 (0.60%)
Hormone receptor +	0	0	1,132 (35.85%)
Hormone receptor -	0	0	0

Characteristics	TCGA	ICGC	COSMIC
Unknown	123 (100%)	1,237 (72.17%)	1,569 (49.68%)
Sequencing data type			
WGS	0	679 (49.61%)	70 (2.22%)
WES	123 (100%)	1,035 (60.38%)	9 (0.28%)
Target sequencing	0	0	3,079 (97.50%)

2. Mutational landscapes of *BRCA1*-positive and -negative samples

2.1 Variant type

To compare variant types between *BRCA1*-positive and -negative samples, we classified all somatic mutations, from both coding and non-coding regions, into single nucleotide variation (SNV), deletion (DEL), insertion (INS), and others. "Others" comprised of mutations that cannot be classified into any previous categories. Insertion and deletion size from ICGC were less than 200 bp. We found that SNV was the majority in *BRCA1*-positive (TCGA 1,475/1,558; 94.67%, ICGC 92,951/97,282; 95.54%, COSMIC 27,057/28,643; 94.46%) and *BRCA1*-negative samples (TCGA 12,894/13,749; 93.78%, ICGC 2,569,039/2,703,478; 95.03%, COSMIC 9,445/12,214; 77.31%) in all databases (Figure 9a, b).

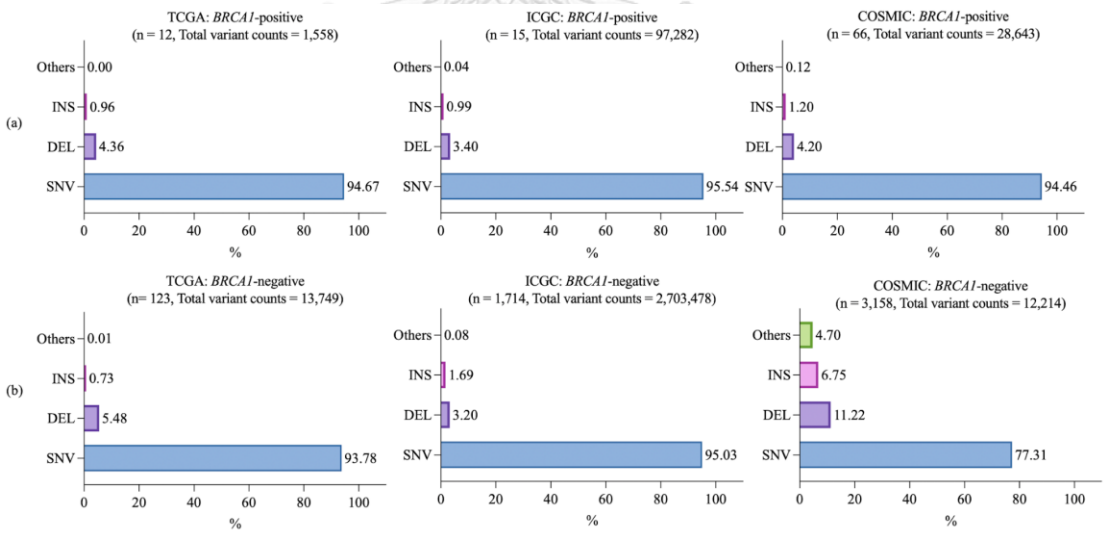


Figure 9 Variant type (a) *BRCA1*-positive (b) *BRCA1*-negative (x-axis: variant type, y-axis: percentage of variant type in database)

2.2 Single nucleotide variants classification

Among these SNVs, C>T was found most abundant in both *BRCA1*-positive (TCGA 539/1,475; 36.54%, ICGC 32,619/92,951; 35.09%, COSMIC 7,059/27,057; 26.08%) and *BRCA1*-negative samples (TCGA 6,129/12,894;

47.53%, ICGC 844,924/2,569,039; 32.88%, COSMIC 4,008/9,445; 42.43%) (Figure 10a, b). The second most abundant SNV was C>G in *BRCA1*-positive samples of all databases. (TCGA 358/1,475; 24.27%, ICGC 29,438/92,951; 31.65%, COSMIC 5,641/27,057; 20.84%) (Fig. 10a). However, the second most abundant SNV in *BRCA1*-negative samples were varied among databases with C>G, C>A and T>C being the second most abundant SNVs in TCGA (3,807/12,894; 29.52%), ICGC (543,067/2,569,039; 21.13%) and COSMIC (1,725/9,445; 18.26%), respectively (Figure 10b). This showed that SNV is the major variant type with C>T mutations being the most abundant SNV in both *BRCA1*-positive and -negative samples.

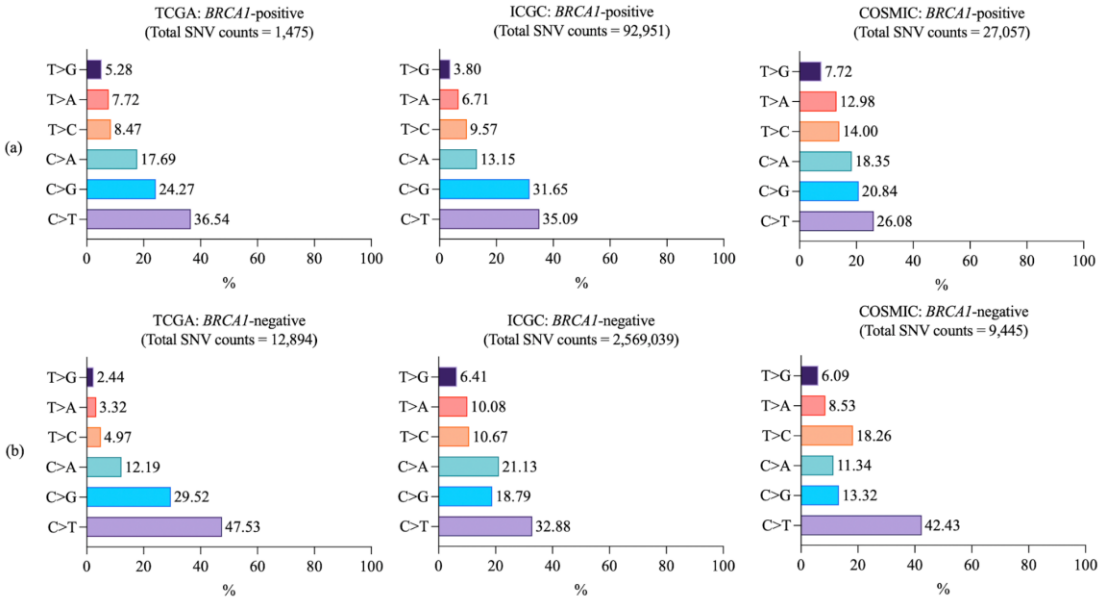


Figure 10 SNV classification (a) *BRCA1*-positive (b) *BRCA1*-negative (x-axis: SNV type, y-axis: percentage of SNV type in database)

2.3 Variant classification

We classified the mutations at coding regions into 7 types; missense, synonymous, nonsense, frameshift deletion, in-frame deletion, frameshift insertion and in-frame insertion. We found that missense mutation was the most abundant mutation found at coding regions in both *BRCA1*-positive (TCGA 993/1,558; 63.86%, ICGC 1,797/97,282; 1.85%, COSMIC 258/28,643; 0.90%) and *BRCA1*-negative (TCGA 8,528/13,749; 62.03%, ICGC 88,553/2,703,478; 3.28%, COSMIC 6,804/12,214; 55.71%) in all databases, followed by synonymous mutations in TCGA and ICGC (Figure 11a, b). However, COSMIC databases showed frameshift deletions to be the second most abundant mutation in both *BRCA1*-positive and *BRCA1*-negative samples (Figure 11a, b). Taken together, Missense mutation is the most abundant variant type in coding regions in both *BRCA1*-positive and -negative samples.

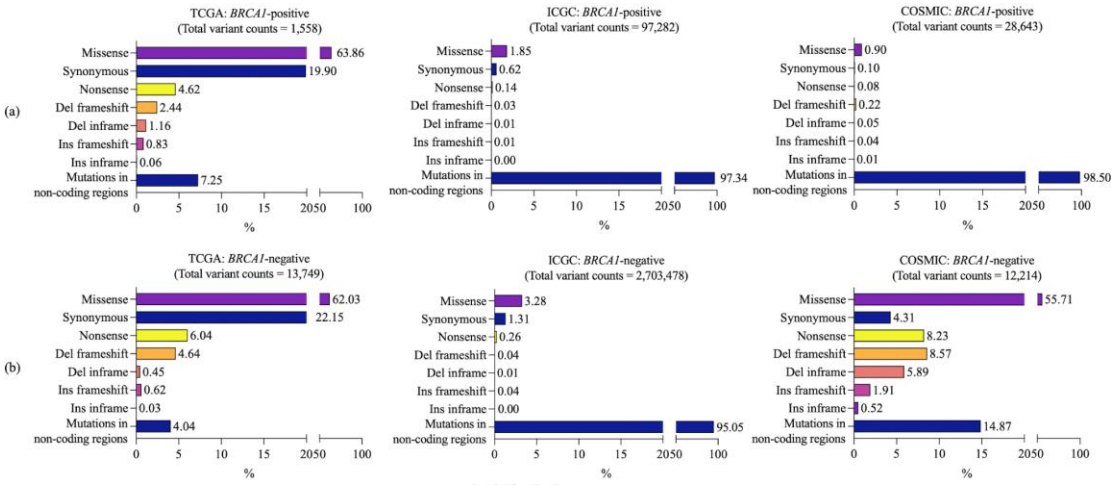


Figure 11 Coding-region variant classification (a) *BRCA1*-positive (b) *BRCA1*-negative (Ins inframe = inframe insertion, Ins frameshift = frameshift insertion, Del inframe = inframe deletion, Del frameshift = frameshift deletion)

2.4 Variant counts

To assess tumor mutational burden of *BRCA1*-positive and -negative samples, we compared coding-region non-synonymous variant count per sample from each group within the same database. We excluded samples which were analyzed by targeted sequencing in COSMIC database. Therefore, 20 *BRCA1*-positive and 79 *BRCA1*-negative from COSMIC were analyzed. We found that the median of total variant counts in *BRCA1*-positive samples were 83.50 ($Q_1$59.75-$Q_3$140.25), 95.00 ($Q_1$66.00-$Q_3$140.00), 6.50 ($Q_1$4.00-$Q_3$8.00) in TCGA, ICGC and COSMIC databases, respectively (Figure 12a). For *BRCA1*-negative samples, the median of variant counts in TCGA, ICGC and COSMIC databases were 39.00 ($Q_1$22.00-$Q_3$65.00), 36.00 ($Q_1$23.00-$Q_3$62.00), and 2.00 ($Q_1$1.00-$Q_3$2.00), respectively (Figure 12b). We found significant differences in total non-synonymous variant counts between *BRCA1*-positive and *BRCA1*-negative samples in all databases (2-tailed p-value: <0.001 in TCGA, <0.001 in ICGC and 0.032 in COSMIC. We also found significant differences in both SNV and indel counts between BRCA1-positive and -negative groups in all databases (p-value <0.001, <0.001 and <0.001 in TCGA, ICGC, COSMIC for SNV count and 0.019, 0.032 and 0.031 in TCGA, ICGC, COSMIC for indel count.) (Supplementary table 1).

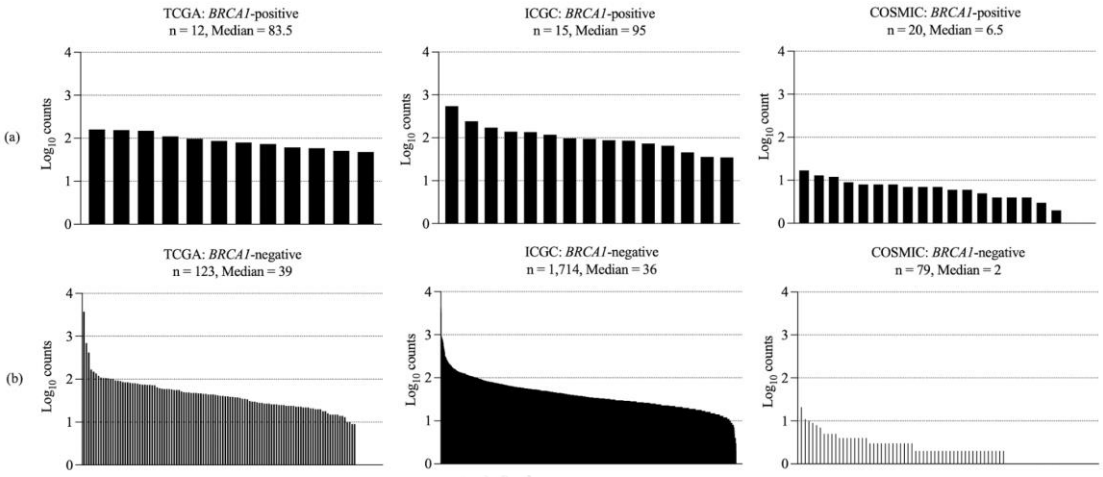


Figure 12 Total count of non-synonymous variant per sample (a) *BRCA1*-positive (b) *BRCA1*-negative (x-axis: each sample arranging by numbers from largest to smallest from left to right, y-axis: $\log_{10}$(variant counts of each sample).

3. Frequently mutated genes in *BRCA1*-positive and -negative breast cancer samples

We found that *TP53* was the most frequently mutated gene in *BRCA1*-positive samples and was accounted for 75.00% (9/12), 60% (9/15) and 59.09% (39/66) in TCGA, ICGC and COSMIC, respectively (Figure 13a). *TTN* was the other top mutated gene in ICGC (9/15, 60%) and was the second most mutated gene in TCGA (6/12, 50.00%) but was not be reported among top mutated genes in COSMIC. For *BRCA1*-negative samples, *TP53* and *PIK3CA* were the most frequently mutated genes in TCGA (TP53: 46/123, 37.39%, PIK3CA: 37/123, 30.08%) and COSMIC (TP53: 955/3,158, 30.24%, PIK3CA: 1247/3,158, 39.48%) and were also found in top 10 most frequently mutated genes in ICGC (TP53: 555/1,714, 32.38%, PIK3CA: 583/1,714, 34.01%) (Figure 13b). *CSMD1* was the most mutated gene in ICGC (627/1,714, 36.58%) and was in the top 20 mutated genes in TCGA (7/123: 5.69%) but was not among the most frequently mutated gene in COSMIC (Figure 13b). This can be summarized that *TP53* and *TTN* were the most frequently mutated genes in *BRCA1*-positive samples, whereas *PIK3CA* and *TP53* were the most frequently mutated genes in *BRCA1*-negative samples. This may reflect different mutational pathways between *BRCA1*-positive and *BRCA1*-negative samples.

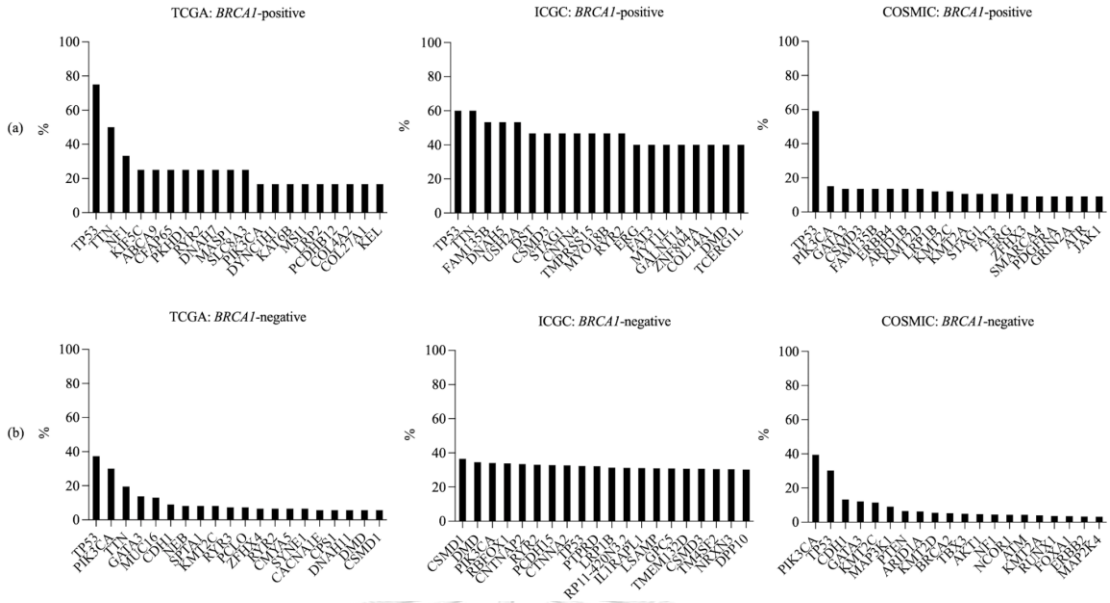


Figure 13 Top mutated genes (a) *BRCA1*-positive (b) *BRCA1*-negative (x-axis: each gene arranging by numbers from largest to smallest from left to right, y-axis: percentage of samples which harbor gene mutation)

4. Recurrent somatic mutations in *BRCA1*-positive and *BRCA1*-negative breast cancer samples

To propose candidate neoantigens for generalized breast cancer vaccine development, in both *BRCA1*-positive and *BRCA1*-negative samples, we looked at the top recurrent somatic mutations exclusively at coding regions (Figure 14a, b). We found Missense *PIK3CA* H1047R, E545K, N345K and E542K consistently across all databases in *BRCA1*-negative samples. *PIK3CA* H1047R was reported in *BRCA1*-negative samples of all databases (TCGA 15/123; 12.19%, ICGC 198/1,714; 11.55% and COSMIC 488/3,158; 15.45%) but was reported at various prevalence in *BRCA1*-positive samples (TCGA: 2/12, 16.67%, ICGC: 0/15, 0%, COSMIC: 3/66, 4.54%). *PIK3CA* E545K and *PIK3CA* N345K was identified in *BRCA1*-negative samples with approximately the same prevalence in all databases (E545K 5.69-7.63%, N345K 1.69-3.25%) but was rarely found in *BRCA1*-positive samples (E545K 0-1.51%, N345K 0%), whereas *PIK3CA* E542K were identified at approximately the same prevalence in both *BRCA1*-positive (4.54-6.67%) and -negative (2.43-4.78%) in all databases. This showed that while the recurrent coding-region mutations are still inconclusive for *BRCA1*-positive samples, *PIK3CA* H1047R, E545K, N345K and E542K were consistently identified across all databases for *BRCA1*-negative samples and, therefore, may be used as the common target neoantigens for *BRCA1*-negative breast cancer vaccine.

Targeting more neoantigens at a time may provide more coverage for generalized breast cancer vaccine. Therefore, we also calculated cumulative coverage of recurrent mutations in both types of samples (Figure 14c, d). In *BRCA1*-positive samples, we found that top 5 somatic mutations as displayed in the graph can cover 41.66% of all samples and top 12 somatic mutations to cover 83.33% of the sample in TCGA; top 6 somatic mutations to cover 26.67% and top 17 to cover 66.67% of the samples in ICGC; and lastly, top 5 to cover 19.69% and top 20 to cover 24.24% of the samples in COSMIC (Figure 14c). For *BRCA1*-negative samples, we found that top 5 somatic mutations as displayed in the graph to cover 26.01% of all samples and top 20 somatic mutations to cover 33.33%

of the sample in TCGA; top 5 somatic mutations to cover 25.37% and top 20 to cover 36.34% of the samples in ICGC; and lastly, top 5 to cover 33.91% and top 20 to cover 45.18% of the samples in COSMIC (Figure 14d).

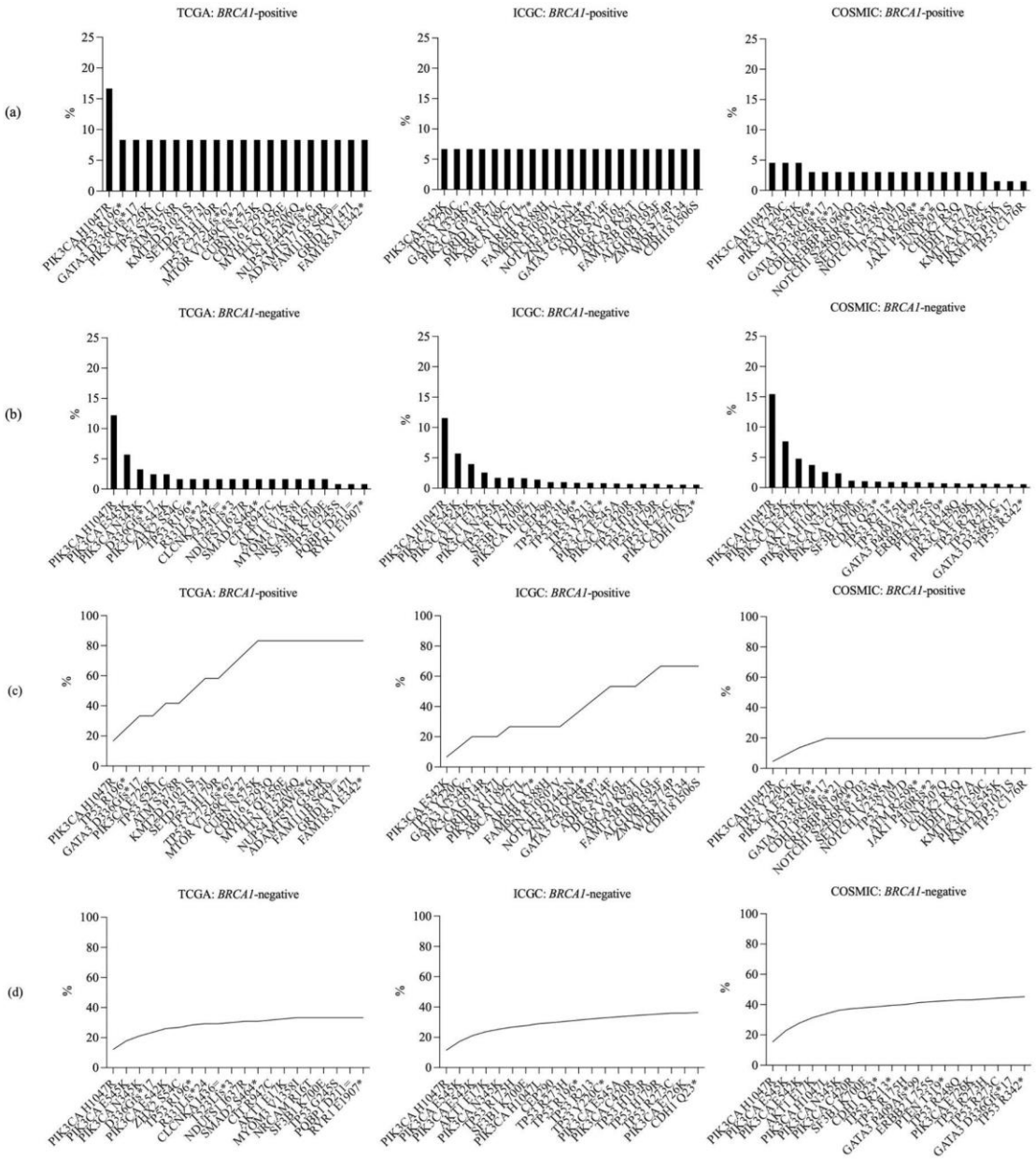


Figure 14 (a) top recurrent somatic mutations of *BRCA1*-positive samples (b) top recurrent somatic mutations of *BRCA1*-negative samples (c) cumulative coverage of recurrent mutations in *BRCA1*-positive samples (d) cumulative coverage of recurrent mutations in *BRCA1*-negative samples

5. **Recurrent somatic mutations in germline *BRCA1*-mutated breast cancer samples**

Next, we aimed to identify candidate neoantigens to be used as preventive cancer vaccine for germline *BRCA1* carriers. We identified 3 studies that reported next-generation sequencing data on samples confirmed to be germline *BRCA1* mutations. Those studies were conducted by Nik-Zanial et al. (2016) [12], by Nones et al. (2019) [66] and by Inagaki-Kawata et al. (2020) [65]. Summary of sample characteristics were shown in Supplementary table 2. Seventy-eight total samples were obtained and analyzed separately. We found that missense *TP53* R175H was consistently the most frequent somatic mutations in all studies and was accounted for 6.45%, 11.53% and 9.52% in study of Nik-Zanial et al. (2016), Nones et al. (2019), and Inagaki-Kawata et al. (2020), respectively (Figure15). Interestingly, *TP53* R175H was not found among the top 20 somatic mutations in all *BRCA1*-positive and -negative studies of ICGC and TCGA.

To compare recurrent mutations from germline *BRCA1*-mutated samples to those identified in *BRCA1*-positive/-negative samples, we found that missense *PIK3CA* H1047R mutation, which are one of the most frequently recurrent in both *BRCA1*-positive and *BRCA1*-negative studies, was rarely found in germline *BRCA1*-mutated samples (Nik-Zanial et al.: 0%, Nones et al.: 3.84%, Inagaki-Kawata et al.: 4.76%). Moreover, other frequently found somatic mutations in *BRCA1*-negative studies were also rarely found in germline *BRCA1*-mutated studies: missense *PIK3CA* E545K (Nik-Zanial et al.: 3.22%, Nones et al.: 0%, Inagaki-Kawata et al: 0%), missense *PIK3CA* E542K (Nik-Zanial et al.: 6.45%, Nones et al.: 0%, Inagaki-Kawata et al: 0%), missense *PIK3CA* N345K (Nik-Zanial et al.: 0%, Nones et al.: 0%, Inagaki-Kawata et al: 0) (Figure 15). This may indicate unique mutational consequences among samples with germline *BRCA1* mutations, non-specific *BRCA1*-positive mutations and no *BRCA1* mutations.

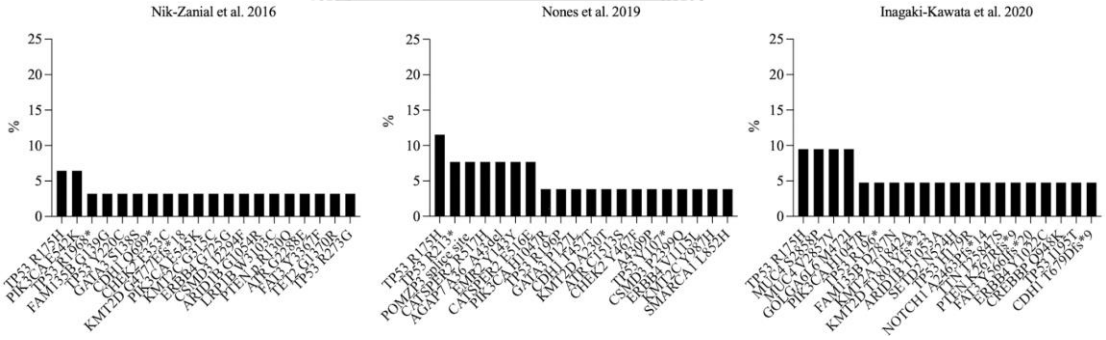


Figure 15 Top recurrent somatic mutations of germline *BRCA1*-mutated breast cancer studies

6. Predicted Antigenicity of top recurrent mutations

We investigated the antigenic potential of mutated proteins from top recurrent somatic by calculating their epitope's binding affinities with MHC class I. The calculated binding affinities of top recurrent mutations were obtained from NetMHCpan BA 4.1 and NetMHCpan EL 4.1 [61, 71]. The candidate recurrent mutations are predicted to be antigenic when their binding affinity was lower than 500 nM [73] (Table 5). We found that most recurrent

mutations are predicted to be antigenic except for *TP53* R175H. For binding affinities with MHC class II, we found that most recurrent mutations are predicted to be antigenic except for *PIK3CA* E542K (Supplementary table 3). Combination of *PIK3CA* H1047R, E542K, E545K and N345K can cover 10.75% (10/93) of *BRCA1*-positive samples, and 27.50% (1,374/4,995) of *BRCA1*-negative samples. It is noteworthy that combination of these recurrent neoantigens can cover minimal to no samples with germline *BRCA1* mutations.

Table 5 Binding prediction results between epitopes of recurrent somatic mutation and MHC class I

Somatic mutation	Peptide	Length	IC 50 (NetMHCpan BA)	Percentile rank (NetMHCpan EL)	HLA type	Allele frequency (%)
TP53 R175H	-	-	-	-	-	-
PIK3CA H1047R	ARHGGWTTK	9	152.47	0.08	HLA-B*27:05	1.82
	ARHGGWTTKM	10	149.04	0.15	HLA-B*27:05	1.82
	DARHGGWTTK	10	389.83	0.87	HLA-A*68:01	3.2
	EYFMKQMNDAR	11	37.03	0.08	HLA-A*33:01	1.9
	EYFMKQMNDAR	11	64.4	0.21	HLA-A*33:03	3.28
	FMKQMNDAR	9	137.91	1.3	HLA-A*31:01	2.35
	FMKQMNDAR	9	120.02	0.47	HLA-A*33:01	1.9
	FMKQMNDAR	9	68.14	0.54	HLA-A*33:03	3.28
	FMKQMNDAR	9	237.4	2.5	HLA-A*68:01	3.2
	KQMNDARHG	9	441.74	3.9	HLA-B*15:03	0.95
	LEYFMKQMNDAR	12	228.99	1.9	HLA-A*33:01	1.9
	MNDARHGGWTTK	12	327.8	0.93	HLA-B*27:05	1.82
	RHGGWTTKM	9	331.38	0.66	HLA-B*15:03	0.95
	YFMKQMNDAR	10	172.46	1.7	HLA-A*31:01	2.35
	YFMKQMNDAR	10	65.48	0.41	HLA-A*33:01	1.9
	YFMKQMNDAR	10	51.2	0.51	HLA-A*33:03	3.28
PIK3CA E542K	KITEQEKDFLW	11	73.72	0.18	HLA-B*58:01	3.53
	KITEQEKDFLW	11	175.22	0.15	HLA-B*57:01	2.33

Somatic mutation	Peptide	Length	IC 50 (NetMHCpan BA)	Percentile rank (NetMHCpan EL)	HLA type	Allele frequency (%)
	KITEQEKDFLW	11	348.41	0.25	HLA-B*57:03	0.51
	KITEQEKDFLW	11	447.72	0.21	HLA-B*57:04	3.76
	SKITEQEKDFLW	12	158.37	0.12	HLA-B*44:02	3.76
	SKITEQEKDFLW	12	303.91	0.19	HLA-B*44:03	3.42
PIK3CA E545K	EITKQEKDFLW	11	194.76	0.26	HLA-B*57:01	2.33
	EITKQEKDFLW	11	391.32	0.64	HLA-B*58:01	3.53
	ITKQEKDFLW	10	87.18	0.35	HLA-B*15:17	1.15
	ITKQEKDFLW	10	14.11	0.01	HLA-B*57:01	2.33
	ITKQEKDFLW	10	83.49	0.06	HLA-B*57:02	0.28
	ITKQEKDFLW	10	29.83	0.03	HLA-B*57:03	0.51
	ITKQEKDFLW	10	49.48	0.02	HLA-B*57:04	0.19
	ITKQEKDFLW	10	13.03	0.04	HLA-B*58:01	3.53
	ITKQEKDFLWS	11	475.1	0.39	HLA-B*57:01	2.33
	KQEKDFLWSHR	11	415.9	1.3	HLA-A*31:01	2.35
	SEITKQEKDF	10	183.55	0.03	HLA-B*44:02	3.76
	SEITKQEKDF	10	295.43	0.05	HLA-B*44:03	3.42
	SEITKQEKDFLW	12	37.97	0.03	HLA-B*44:02	3.76
	SEITKQEKDFLW	12	47.3	0.06	HLA-B*44:03	3.42
PIK3CA N345K	ATYVKVNIR	9	18.66	0.04	HLA-A*31:01	2.35
	ATYVKVNIR	9	95.92	0.34	HLA-A*68:01	3.2
	ATYVKVNIR	9	141.06	0.22	HLA-A*11:01	12.96
	ATYVKVNIR	9	141.06	0.22	HLA-A*11:02	1.75
	ATYVKVNIR	9	177.13	0.21	HLA-A*33:03	3.28
	ATYVKVNIR	9	315.27	0.26	HLA-A*34:02	0.63
	ATYVKVNIR	9	471.91	0.06	HLA-A*74:01	1.26

Somatic mutation	Peptide	Length	IC 50 (NetMHCpan BA)	Percentile rank (NetMHCpan EL)	HLA type	Allele frequency (%)
	CATYVKVNI	9	350.92	2.1	HLA-A*68:02	1.51
	CATYVKVNIR	10	49.13	2.3	HLA-A*68:01	3.2
	CATYVKVNIR	10	141.44	1.8	HLA-A*31:01	2.35
	CATYVKVNIR	10	160.9	1.8	HLA-A*33:03	3.28
	CATYVKVNIR	10	421.26	1.9	HLA-A*33:01	1.9
	IKILCATYVK	10	87.01	2.9	HLA-A*03:02	2.33
	IKILCATYVK	10	91.23	3	HLA-A*11:01	12.96
	IKILCATYVK	10	91.23	3	HLA-A*11:02	1.75
	IKILCATYVK	10	219.49	3.7	HLA-A*03:01	7.29
	IKILCATYVK	10	442.75	7.2	HLA-A*34:02	0.63
	ILCATYVKV	9	49.53	0.7	HLA-A*02:03	3.28
	ILCATYVKV	9	53.62	0.8	HLA-A*02:02	1.87
	ILCATYVKV	9	80.57	0.58	HLA-A*02:01	15.67
	ILCATYVKV	9	206.48	1.3	HLA-A*02:06	1.82
	ILCATYVKV	9	459.32	2	HLA-A*02:05	1.1
	KILCATYVK	9	16.81	0.42	HLA-A*11:01	12.96
	KILCATYVK	9	16.81	0.42	HLA-A*11:02	1.75
	KILCATYVK	9	18.78	0.32	HLA-A*03:02	2.33
	KILCATYVK	9	39.61	0.53	HLA-A*03:01	7.29
	KILCATYVK	9	48.12	0.56	HLA-A*30:01	2.98
	KILCATYVK	9	98.38	2.1	HLA-A*31:01	2.35
	KILCATYVK	9	259.48	0.54	HLA-A*74:01	1.26
	KILCATYVKV	10	83.05	3.1	HLA-A*02:06	1.82
	KILCATYVKV	10	142.15	2.7	HLA-A*02:01	15.67
	KILCATYVKV	10	215.49	3.8	HLA-A*02:03	3.28
	KILCATYVKV	10	246.16	5.1	HLA-A*02:02	1.87

Somatic mutation	Peptide	Length	IC 50 (NetMHCpan BA)	Percentile rank (NetMHCpan EL)	HLA type	Allele frequency (%)
	KVNIRDIDK	9	140.22	0.44	HLA-A*30:01	2.98
	KVNIRDIDK	9	319.19	0.71	HLA-A*11:01	12.96
	KVNIRDIDK	9	319.19	0.71	HLA-A*11:02	1.75
	KVNIRDIDK	9	409.79	0.63	HLA-A*03:02	2.33
	KVNIRDIDK	9	478.35	0.6	HLA-A*03:01	2.98
	LRIKILCATYVK	12	109.9	1.5	HLA-B*27:05	1.82
	RIKILCATYVK	11	59.05	0.64	HLA-A*30:01	2.98
	RIKILCATYVK	11	130.18	1.5	HLA-A*03:02	2.33
	RIKILCATYVK	11	142.46	2.1	HLA-A*11:01	12.96
	RIKILCATYVK	11	142.46	2.1	HLA-A*11:02	1.75
	RIKILCATYVK	11	216.66	1.4	HLA-A*03:01	7.29
	RIKILCATYVK	11	251.11	2.4	HLA-A*31:01	2.35
	RIKILCATYVKV	12	281.45	4.7	HLA-A*30:01	2.98
	TYVKVNIRDI	10	170.7	0.81	HLA-A*24:03	0.69
	TYVKVNIRDI	10	399.23	0.77	HLA-A*23:01	3.14
	YVKVNIRDI	9	309.24	0.66	HLA-C*12:03	4.97

CHAPTER IV

DISCUSSION

Personalized neoantigen-based cancer vaccine revolutionized personalized medicine [85]; however, its highly-individualized manufacturing process may hinder its accessibility by all. Shared neoantigen vaccine have certain advantages over personalized approach in cases where the time and resources are limited and patients with aggressive diseases who cannot afford delay of treatment. In this study, we identified recurrent somatic mutations and potential shared candidate neoantigens in *BRCA1*-positive, -negative and germline *BRCA1*-mutated breast cancer. We analyzed mutation data of the breast cancer samples with and without "pathogenic" or "likely pathogenic" *BRCA1* mutation as determined by ACMG 2015 criteria (referred to as *BRCA1*-positive and -negative, respectively) that were available on 3 public cancer databases; TCGA, ICGC and COSMIC). We also reported mutation landscapes, recurrent mutated genes in *BRCA1*-positive and -negative samples.

Our findings on mutational landscapes correspond with previous studies. Our results showed that SNV is the most abundant variant type in both *BRCA1*-positive and -negative groups and C>T is the most abundant SNV mutation type in both groups. This finding is agreeable among all databases which corresponds with finding by Zámborszky and colleagues. They reported that C>T is the most common SNV in both wild-type *BRCA1* and mutated *BRCA1* cell lines. They also reported no major shift in proportion of C>T and other SNV type between two groups [86]. The results corresponded with previous study which reported that most common spontaneous mutagenetic process in vertebrate genome was C>T change and caused by the deamination of 5-methyl-cytosine at CpG site [87]. Mutational burden represented by total variant counts showed differences between *BRCA1*-positive and -negative among all databases; furthermore, *BRCA1*-positive group harbored more SNVs and indels compared to *BRCA1*-negative group. (Supplementary table 1) This also corresponds with finding by Nolan and colleagues who analyzed tumor mutational burden by WES and found a marked enrichment of missense and indel mutations in *BRCA1*-mutated triple-negative breast cancer compared to non *BRCA1*-mutated group [88]. The explanation of BRCA1 dysfunction and cancer development is that BRCA1 plays a major role in double strand break (DSB) DNA repair which used double strand DNA as a template and was known as 'error-free repair'. BRCA1 is important in error-free DNA repair and explain why the loss of BRCA1 function produces a vast number of mutations [53, 54].

We reported shared neoantigens *PIK3CA* H1047R, *PIK3CA* E545K, *PIK3CA* E542K, and *PIK3CA* N345K to be found approximately 27.50% among BRCA1-negative samples. Previous studies reported that *PIK3CA* H1047R are found recurrently among breast cancer of unspecified genotype [89]. In this study, we found that the same set of neoantigens may not cover either somatic or germline *BRCA1*-mutated breast cancer. For *BRCA1*-positive breast cancer, recurrent mutations were inclusive. It may caused by sample size of *BRCA1*-positive samples was too small to detect recurrent mutations. Interestingly, *TP53* R175H is found to be the top recurrent mutation among 3 germline *BRCA1* studies but is not found among *BRCA1*-positive or -negative samples. *TP53* R175H was not predicted to be antigenic by NetMHCpan; however, it was proven to be antigenic by *in vitro* single-chain diabody **(**scDb**)** co-incubation assays [90, 91]. Our findings provided list of candidate neoantigens which may be used for off-the-shelf

cancer vaccine, both for therapeutic purposes for cases with somatic *BRCA1* mutations and for prevention purposes for those with germline *BRCA1* mutations.

CHAPTER V

CONCLUSION

In this study, we identified mutational landscape of *BRCA1*-related breast cancer. We found no distinctive difference in variant type and SNV classification between *BRCA1*-positive and -negative breast cancer. For variant count, *BRCA1*-positive group significantly harbored more total variant counts, SNVs and indels than *BRCA1*-negative group. For frequently mutated genes, TP53 and TTN were the most frequently mutated genes in BRCA1-positive samples, whereas PIK3CA and TP53 were the most frequently mutated genes in BRCA1-negative samples. This may reflect different mutational pathways between BRCA1-positive and BRCA1-negative samples.

Furthermore, we identified shared neoantigens for somatic, germline *BRCA*1 mutations and *BRCA1*-wild type breast cancer using 3 different public cancer databases. We found that *PIK3CA* H1047R, *PIK3CA* E545K, *PIK3CA* E542K, and *PIK3CA* N345K to be found approximately 27.50% (1,374/4,995) among *BRCA1*-negative samples while the same set of neoantigen can cover approximately 10.75% (10/93) of somatic *BRCA1*-positive samples and 6.41% (5/78) of germline *BRCA1* mutation breast cancer. *TP53* R175H was the top shared neoantigen for germline *BRCA1* mutation that was not found in the other groups. Because these mutations produced antigenic peptides which can be recognized by multiple HLA molecules, these mutations have potential to be candidate neoantigen targets for neoantigen-based cancer vaccine.

APPENDIX

Supplementary table 1 Median and p-value of non-synonymous variant from Mann-Whitney U test of all databases

Type of counts	*BRCA1*- positive (median)	*BRCA1*- negative (median)	p-value (2-tailed)
TCGA			
Total variant count	83.50 (Q_1 59.75-$Q_3$140.25)	39.00 ($Q_1$22.00-$Q_3$65.00)	<0.001
SNV count	80.00 ($Q_1$53.00-$Q_3$137.25)	36.00 ($Q_1$19.00-$Q_3$56.00)	<0.001
Indel count	5.50 ($Q_1$2.00-$Q_3$9.00)	3.00 ($Q_1$1.00-$Q_3$4.00)	0.019
ICGC			
Total variant count	95.00 ($Q_1$66.00-$Q_3$140.00)	36.00 ($Q_1$23.00-$Q_3$62.00)	<0.001
SNV count	91.00 ($Q_1$63.00-$Q_3$139.00)	34.00 ($Q_1$22.00-$Q_3$60.00)	<0.001
Indel count	2.00 ($Q_1$0.00-$Q_3$6.00)	1.00 ($Q_1$0.00-$Q_3$2.00)	0.032
COSMIC			
Total variant count	6.50 ($Q_1$4.00-$Q_3$8.00)	2.00 ($Q_1$1.00-$Q_3$2.00)	<0.001
SNV count	5.00 ($Q_1$2.50-$Q_3$7.00)	1.00 ($Q_1$1.00-$Q_3$2.00)	<0.001
Indel count	1.00 ($Q_1$0.00-$Q_3$2.00)	0.00 ($Q_1$0.00-$Q_3$1.00)	0.031

Supplementary Table 2 Sample characteristics of germline *BRCA1*-mutated breast cancer studies

	Nik-Zanial et al. 2016	Nones et al. 2019	Inagaki-Kawata et al. 2020
Analysis type	WGS	WGS	Targeted sequencing of 115 genes associated with breast cancer
Platform	Illumina Hiseq 2000/2500	Illumina X-Ten	SureSelect system (Agilent)
Samples	31	26	21
Raw data	EGAS00001001178 (the European-Genome Phenome Archive)	EGAS00001003305 (the European-Genome Phenome Archive)	EGAS00001004630, EGAS00001004182 (the European-Genome Phenome Archive)

Supplementary Table 3 Binding prediction results between epitopes of recurrent somatic mutation and MHC class II

Somatic mutation	Allele	Peptide	Length	Method	Adjusted percentile rank	IC50	Allele frequency (%)
PIK3CA E542K	-	-	-	-	-	-	-
PIK3CA E545K	HLA-DRB1*07:01	KQEKDFLWSHRHYCV	15	Consensus	8.3	-	12.21
	HLA-DPA1*01:03 /DPB1*04:01	KQEKDFLWSHRHYCVTI	17	NetMHCIIpan	44.28	881.39	17.41
	HLA-DPA1*01:03 /DPB1*04:01	KQEKDFLWSHRHYCVTIP	18	NetMHCIIpan	85.83	904.49	17.41
	HLA-DPA1*01:03 /DPB1*04:01	TKQEKDFLWSHRHYCVTI	18	NetMHCIIpan	82.87	875.65	17.41
PIK3CA H1047R	HLA-DRB1*04:01	ALEYFMKQMNDAHR	14	Consensus	4.85	-	6.37
	HLA-DRB1*04:01	ALEYFMKQMNDAHRG	15	Consensus	5.2	-	6.37
	HLA-DRB3*02:02	ALEYFMKQMNDAHRG	15	NetMHCIIpan	14	850.37	16.40
	HLA-DRB1*04:01	ALEYFMKQMNDAHRGG	16	Consensus	6.93	-	6.37
	HLA-DRB3*02:02	ALEYFMKQMNDAHRGG	16	NetMHCIIpan	17.31	936.09	16.40
	HLA-DRB1*04:01	EALEYFMKQMNDAHR	15	Consensus	5.2	-	6.37
	HLA-DRB1*04:01	EALEYFMKQMNDAHRG	16	Consensus	6.93	-	6.37
	HLA-DRB3*02:02	EALEYFMKQMNDAHRG	16	NetMHCIIpan	18.47	989.67	16.40
	HLA-DPA1*01:03 /DPB1*04:01	EQEALEYFMKQMNDAHR	17	NetMHCIIpan	28.96	537.46	17.41
	HLA-DPA1*01:03 /DPB1*04:01	EQEALEYFMKQMNDAHRG	18	NetMHCIIpan	59.19	581.18	17.41
	HLA-DRB1*04:01	EYFMKQMNDAHR	12	Consensus	8.9	-	6.37
	HLA-DRB1*04:01	EYFMKQMNDAHRG	13	Consensus	6.08	-	6.37
	HLA-DRB1*04:01	EYFMKQMNDAHRGG	14	Consensus	4.85	-	6.37
	HLA-DRB1*04:01	EYFMKQMNDAHRGGW	15	Consensus	5.2	-	6.37

HLA-DRB3*02:02	EYFMKQMNDAHRGGW	15	NetMHCIIpan	15	929.56	16.40
HLA-DRB1*04:01	EYFMKQMNDAHRGGWT	16	Consensus	6.93	-	6.37
HLA-DRB3*01:01	HRGGWTTKMDWIFHT	15	Consensus	9.1	-	18.00
HLA-DRB1*04:01	LEYFMKQMNDAHR	13	Consensus	6.08	-	6.37
HLA-DRB1*04:01	LEYFMKQMNDAHRG	14	Consensus	4.85	-	6.37
HLA-DRB3*02:02	LEYFMKQMNDAHRG	14	NetMHCIIpan	12.92	960.74	16.40
HLA-DRB1*04:01	LEYFMKQMNDAHRGG	15	Consensus	5.2	-	6.37
HLA-DRB3*02:02	LEYFMKQMNDAHRGG	15	NetMHCIIpan	14	842.99	16.40
HLA-DRB1*04:01	LEYFMKQMNDAHRGGW	16	Consensus	6.93	-	6.37
HLA-DRB3*02:02	LEYFMKQMNDAHRGGW	16	NetMHCIIpan	16.16	864.52	16.40
HLA-DPA1*01:03 /DPB1*04:01	QEALEYFMKQMNDAHR	16	NetMHCIIpan	21.93	703.46	17.41
HLA-DRB1*04:01	QEALEYFMKQMNDAHR	16	Consensus	6.93	-	6.37
HLA-DPA1*01:03 /DPB1*04:01	QEALEYFMKQMNDAHRG	17	NetMHCIIpan	39.17	790.95	17.41
HLA-DPA1*01:03 /DPB1*04:01	QEALEYFMKQMNDAHRGG	18	NetMHCIIpan	79.91	831.41	17.41
HLA-DRB3*01:01	RGGWTTKMDWIFHT	14	Consensus	7.97	-	18.00
HLA-DRB3*01:01	RGGWTTKMDWIFHTI	15	Consensus	7.6	-	18.00
HLA-DPA1*01:03 /DPB1*04:01	RGGWTTKMDWIFHTIKQH	18	NetMHCIIpan	85.83	902.16	17.41
HLA-DPA1*01:03 /DPB1*04:01	TEQEALEYFMKQMNDAHR	18	NetMHCIIpan	47.35	466.35	17.41
HLA-DRB1*04:01	YFMKQMNDAHRG	12	Consensus	9.79	-	6.37
HLA-DRB1*04:01	YFMKQMNDAHRGG	13	Consensus	6.08	-	6.37
HLA-DRB1*04:01	YFMKQMNDAHRGGW	14	Consensus	4.85	-	6.37
HLA-DRB1*04:01	YFMKQMNDAHRGGWT	15	Consensus	5.8	-	6.37

	HLA-DRB1*04:01	YFMKQMNDAHRGGWTT	16	Consensus	8.43	-	6.37
PIK3CA N345K	HLA-DRB1*01:01	ALRIKILCATYV	12	Consensus	2.43	-	7.54
	HLA-DRB1*08:02	ALRIKILCATYV	12	Consensus	5.63	-	0.68
	HLA-DRB1*01:01	ALRIKILCATYVK	13	Consensus	2.03	-	7.54
	HLA-DRB1*07:01	ALRIKILCATYVK	13	Consensus	5.61	-	12.21
	HLA-DRB1*08:02	ALRIKILCATYVK	13	Consensus	4.52	-	0.68
	HLA-DRB1*12:01	ALRIKILCATYVK	13	Consensus	1.72	-	1.97
	HLA-DRB1*13:02	ALRIKILCATYVK	13	Consensus	8.73	-	4.60
	HLA-DRB1*15:01	ALRIKILCATYVK	13	Consensus	2.49	-	11.16
	HLA-DRB3*02:02	ALRIKILCATYVK	13	NetMHCIIpan	11.23	985.45	16.40
	HLA-DRB4*01:01	ALRIKILCATYVK	13	Consensus	6.39	-	28.00
	HLA-DRB5*01:01	ALRIKILCATYVK	13	Consensus	7.48	-	16.10
	HLA-DPA1*01:03 /DPB1*02:01	ALRIKILCATYVKV	14	Consensus	7.32	-	15.31
	HLA-DPA1*01:03 /DPB1*04:01	ALRIKILCATYVKV	14	NetMHCIIpan	3.77	281.81	17.41
	HLA-DRB1*01:01	ALRIKILCATYVKV	14	Consensus	1.72	-	7.54
	HLA-DRB1*04:05	ALRIKILCATYVKV	14	Consensus	9.58	-	1.16
	HLA-DRB1*07:01	ALRIKILCATYVKV	14	Consensus	4.2	-	12.21
	HLA-DRB1*08:02	ALRIKILCATYVKV	14	Consensus	4.2	-	0.68
	HLA-DRB1*12:01	ALRIKILCATYVKV	14	Consensus	1.56	-	1.97
	HLA-DRB1*13:02	ALRIKILCATYVKV	14	Consensus	5.38	-	4.60
	HLA-DRB1*15:01	ALRIKILCATYVKV	14	Consensus	1.94	-	11.16
	HLA-DRB3*02:02	ALRIKILCATYVKV	14	NetMHCIIpan	7.32	549.59	16.40

HLA-DRB4*01:01	ALRIKILCATYVKV	14	Consensus	5.49	-	28.00
HLA-DRB5*01:01	ALRIKILCATYVKV	14	Consensus	6.25	-	16.10
HLA-DPA1*01:03 /DPB1*02:01	ALRIKILCATYVKVN	15	Consensus	8.2	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	ALRIKILCATYVKVN	15	NetMHCIIpan	4.5	229.91	17.41
HLA-DPA1*02:01 /DPB1*14:01	ALRIKILCATYVKVN	15	NetMHCIIpan	4.2	923.04	11.59
HLA-DRB1*01:01	ALRIKILCATYVKVN	15	Consensus	2	-	7.54
HLA-DRB1*04:05	ALRIKILCATYVKVN	15	Consensus	8.9	-	1.16
HLA-DRB1*07:01	ALRIKILCATYVKVN	15	Consensus	5.4	-	12.21
HLA-DRB1*08:02	ALRIKILCATYVKVN	15	Consensus	5.1	-	0.68
HLA-DRB1*12:01	ALRIKILCATYVKVN	15	Consensus	1.9	-	1.97
HLA-DRB1*13:02	ALRIKILCATYVKVN	15	Consensus	5.7	-	4.60
HLA-DRB1*15:01	ALRIKILCATYVKVN	15	Consensus	2.7	-	11.16
HLA-DRB3*02:02	ALRIKILCATYVKVN	15	NetMHCIIpan	9.1	560.67	16.40
HLA-DRB4*01:01	ALRIKILCATYVKVN	15	Consensus	6.4	-	28.00
HLA-DRB5*01:01	ALRIKILCATYVKVN	15	Consensus	7.1	-	16.10
HLA-DPA1*01:03 /DPB1*04:01	ALRIKILCATYVKVNI	16	NetMHCIIpan	5.08	192.35	17.41
HLA-DPA1*02:01 /DPB1*14:01	ALRIKILCATYVKVNI	16	NetMHCIIpan	6.12	759.96	11.59
HLA-DRB1*01:01	ALRIKILCATYVKVNI	16	Consensus	3.46	-	7.54
HLA-DRB1*07:01	ALRIKILCATYVKVNI	16	Consensus	7.96	-	12.21
HLA-DRB1*08:02	ALRIKILCATYVKVNI	16	Consensus	7.62	-	0.68
HLA-DRB1*12:01	ALRIKILCATYVKVNI	16	Consensus	2.89	-	1.97
HLA-DRB1*13:02	ALRIKILCATYVKVNI	16	Consensus	7.5	-	4.60

HLA-DRB1*15:01	ALRIKILCATYVKVNI	16	Consensus	4.73	-	11.16
HLA-DRB3*02:02	ALRIKILCATYVKVNI	16	NetMHCIIpan	13.85	723.59	16.40
HLA-DRB4*01:01	ALRIKILCATYVKVNI	16	Consensus	8.43	-	28.00
HLA-DPA1*01:03 /DPB1*04:01	ALRIKILCATYVKVNIR	17	NetMHCIIpan	9.54	212.59	17.41
HLA-DPA1*02:01 /DPB1*14:01	ALRIKILCATYVKVNIR	17	NetMHCIIpan	11.07	715.8	11.59
HLA-DRB1*01:01	ALRIKILCATYVKVNIR	17	Consensus	5.96	-	7.54
HLA-DRB1*12:01	ALRIKILCATYVKVNIR	17	Consensus	5.71	-	1.97
HLA-DRB1*15:01	ALRIKILCATYVKVNIR	17	Consensus	9.71	-	11.16
HLA-DRB3*02:02	ALRIKILCATYVKVNIR	17	NetMHCIIpan	22.14	883.35	16.40
HLA-DPA1*01:03 /DPB1*04:01	ALRIKILCATYVKVNIRD	18	NetMHCIIpan	21.01	236.3	17.41
HLA-DPA1*02:01 /DPB1*14:01	ALRIKILCATYVKVNIRD	18	NetMHCIIpan	25.16	760.5	11.59
HLA-DRB1*04:01	ATPYMNGETSTKS	13	Consensus	5.61	-	6.37
HLA-DRB1*04:01	ATPYMNGETSTKSL	14	Consensus	4.52	-	6.37
HLA-DRB1*04:01	ATPYMNGETSTKSLW	15	Consensus	4.7	-	6.37
HLA-DRB1*04:01	ATPYMNGETSTKSLWV	16	Consensus	6.35	-	6.37
HLA-DRB1*01:01	ETSTKSLWVINSALRI	16	Consensus	6.81	-	7.54
HLA-DRB1*08:02	ETSTKSLWVINSALRI	16	Consensus	3.58	-	0.68
HLA-DRB1*15:01	ETSTKSLWVINSALRI	16	Consensus	5.43	-	11.16
HLA-DRB5*01:01	ETSTKSLWVINSALRI	16	Consensus	6.81	-	16.10
HLA-DRB1*08:02	ETSTKSLWVINSALRIK	17	Consensus	5.96	-	0.68
HLA-DRB1*12:01	ETSTKSLWVINSALRIK	17	Consensus	7.83	-	1.97
HLA-DRB1*15:01	ETSTKSLWVINSALRIK	17	Consensus	9.03	-	11.16

HLA-DRB1*12:01	ETSTKSLWVINSALRIKI	18	Consensus	9.62	-	1.97
HLA-DRB3*01:01	ETSTKSLWVINSALRIKI	18	Consensus	9.77	-	18.00
HLA-DRB1*08:02	FTMPSYSRRISTATP	15	Consensus	8.9	-	0.68
HLA-DRB1*08:02	GETSTKSLWVINSALRI	17	Consensus	5.96	-	0.68
HLA-DRB1*15:01	GETSTKSLWVINSALRI	17	Consensus	9.2	-	11.16
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVN	12	NetMHCIIpan	8.9	751	17.41
HLA-DPA1*01:03 /DPB1*02:01	IKILCATYVKVNI	13	Consensus	9.67	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVNI	13	NetMHCIIpan	5.3	451.81	17.41
HLA-DRB1*01:01	IKILCATYVKVNI	13	Consensus	8.73	-	7.54
HLA-DRB1*07:01	IKILCATYVKVNI	13	Consensus	8.11	-	12.21
HLA-DRB1*15:01	IKILCATYVKVNI	13	Consensus	8.11	-	11.16
HLA-DPA1*01:03 /DPB1*02:01	IKILCATYVKVNIR	14	Consensus	8.29	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVNIR	14	NetMHCIIpan	4.74	340.4	17.41
HLA-DRB1*01:01	IKILCATYVKVNIR	14	Consensus	7.97	-	7.54
HLA-DRB1*07:01	IKILCATYVKVNIR	14	Consensus	7.65	-	12.21
HLA-DRB1*15:01	IKILCATYVKVNIR	14	Consensus	8.51	-	11.16
HLA-DPA1*01:03 /DPB1*02:01	IKILCATYVKVNIRD	15	Consensus	9.4	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVNIRD	15	NetMHCIIpan	6.5	307.43	17.41
HLA-DRB1*01:01	IKILCATYVKVNIRD	15	Consensus	9.3	-	7.54
HLA-DRB1*07:01	IKILCATYVKVNIRD	15	Consensus	9.7	-	12.21
HLA-DPA1*01:03 /DPB1*02:01	IKILCATYVKVNIRDI	16	Consensus	9.93	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVNIRDI	16	NetMHCIIpan	9.7	314.87	17.41

HLA-DRB1*01:01	IKILCATYVKVNIRDI	16	Consensus	4.39	-	7.54
HLA-DRB1*07:01	IKILCATYVKVNIRDI	16	Consensus	4.27	-	12.21
HLA-DRB1*09:01	IKILCATYVKVNIRDI	16	Consensus	0.91	-	1.68
HLA-DRB1*11:01	IKILCATYVKVNIRDI	16	Consensus	7.85	-	4.25
HLA-DRB1*13:02	IKILCATYVKVNIRDI	16	Consensus	4.85	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVNIRDID	17	NetMHCIIpan	20.44	373.3	17.41
HLA-DRB1*01:01	IKILCATYVKVNIRDID	17	Consensus	7.49	-	7.54
HLA-DRB1*07:01	IKILCATYVKVNIRDID	17	Consensus	7.15	-	12.21
HLA-DRB1*09:01	IKILCATYVKVNIRDID	17	Consensus	1.62	-	1.68
HLA-DRB1*13:02	IKILCATYVKVNIRDID	17	Consensus	7.83	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	IKILCATYVKVNIRDIDK	18	NetMHCIIpan	41.44	407.26	17.41
HLA-DRB1*09:01	IKILCATYVKVNIRDIDK	18	Consensus	3.26	-	1.68
HLA-DRB1*13:02	ILCATYVKVNIRDIDK	16	Consensus	8.31	-	4.60
HLA-DRB1*01:01	INSALRIKILCATYV	15	Consensus	2.2	-	7.54
HLA-DRB1*08:02	INSALRIKILCATYV	15	Consensus	4	-	0.68
HLA-DRB1*13:02	INSALRIKILCATYV	15	Consensus	8.2	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	INSALRIKILCATYVK	16	NetMHCIIpan	21.93	708.94	17.41
HLA-DQA1*01:02 /DQB1*06:02	INSALRIKILCATYVK	16	Consensus	3.12	-	10.40
HLA-DRB1*01:01	INSALRIKILCATYVK	16	Consensus	3.69	-	7.54
HLA-DRB1*07:01	INSALRIKILCATYVK	16	Consensus	8.43	-	12.21
HLA-DRB1*08:02	INSALRIKILCATYVK	16	Consensus	6.58	-	0.68
HLA-DRB1*12:01	INSALRIKILCATYVK	16	Consensus	3.12	-	1.97

HLA-DRB1*15:01	INSALRIKILCATYVK	16	Consensus	5.66	-	11.16
HLA-DRB4*01:01	INSALRIKILCATYVK	16	Consensus	6.58	-	28.00
HLA-DPA1*01:03 /DPB1*04:01	INSALRIKILCATYVKV	17	NetMHCIIpan	11.41	243.57	17.41
HLA-DPA1*02:01 /DPB1*14:01	INSALRIKILCATYVKV	17	NetMHCIIpan	13.29	808.99	11.59
HLA-DQA1*01:02 /DQB1*06:02	INSALRIKILCATYVKV	17	Consensus	6.81	-	10.40
HLA-DRB1*01:01	INSALRIKILCATYVKV	17	Consensus	5.62	-	7.54
HLA-DRB1*12:01	INSALRIKILCATYVKV	17	Consensus	5.19	-	1.97
HLA-DRB1*15:01	INSALRIKILCATYVKV	17	Consensus	8.52	-	11.16
HLA-DPA1*01:03 /DPB1*04:01	INSALRIKILCATYVKVN	18	NetMHCIIpan	23.97	257.86	17.41
HLA-DPA1*02:01 /DPB1*14:01	INSALRIKILCATYVKVN	18	NetMHCIIpan	26.05	779.32	11.59
HLA-DRB1*12:01	INSALRIKILCATYVKVN	18	Consensus	9.17	-	1.97
HLA-DRB1*04:01	ISTATPYMNGETSTKS	16	Consensus	6.35	-	6.37
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNI	12	NetMHCIIpan	10.38	850.18	17.41
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNIR	13	NetMHCIIpan	7.64	641.18	17.41
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNIRD	14	NetMHCIIpan	7.65	536.93	17.41
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNIRDI	15	NetMHCIIpan	8.8	419.01	17.41
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNIRDID	16	NetMHCIIpan	15.01	450.34	17.41
HLA-DRB1*13:02	KILCATYVKVNIRDID	16	Consensus	8.31	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNIRDIDK	17	NetMHCIIpan	27.25	510.13	17.41
HLA-DPA1*01:03 /DPB1*04:01	KILCATYVKVNIRDIDKI	18	NetMHCIIpan	56.23	528.01	17.41
HLA-DRB1*01:01	KSLWVINSALRI	12	Consensus	8.9	-	7.54

HLA-DRB1*08:02	KSLWVINSALRI	12	Consensus	5.34	-	0.68
HLA-DRB1*03:01	KSLWVINSALRIKI	14	Consensus	9.15	-	9.82
HLA-DRB1*11:01	KSLWVINSALRIKI	14	Consensus	3.98	-	4.25
HLA-DRB1*11:01	KSLWVINSALRIKIL	15	Consensus	4.1	-	4.25
HLA-DRB1*08:02	KSLWVINSALRIKILC	16	Consensus	3.58	-	0.68
HLA-DRB1*11:01	KSLWVINSALRIKILC	16	Consensus	7.16	-	4.25
HLA-DRB1*08:02	KSLWVINSALRIKILCA	17	Consensus	5.96	-	0.68
HLA-DRB1*15:01	KSLWVINSALRIKILCA	17	Consensus	8.01	-	11.16
HLA-DRB1*08:02	KSLWVINSALRIKILCAT	18	Consensus	5.62	-	0.68
HLA-DRB3*01:01	KSLWVINSALRIKILCAT	18	Consensus	9.47	-	18.00
HLA-DRB1*03:01	KVNIRDIDKIYVR	13	Consensus	9.82	-	9.82
HLA-DRB1*03:01	KVNIRDIDKIYVRT	14	Consensus	8.61	-	9.82
HLA-DRB1*03:01	KVNIRDIDKIYVRTG	15	Consensus	9.9	-	9.82
HLA-DRB1*11:01	KVNIRDIDKIYVRTG	15	Consensus	8.7	-	4.25
HLA-DRB1*01:01	LRIKILCATYVK	12	Consensus	2.58	-	7.54
HLA-DRB1*07:01	LRIKILCATYVK	12	Consensus	8.3	-	12.21
HLA-DRB1*08:02	LRIKILCATYVK	12	Consensus	8.01	-	0.68
HLA-DRB1*12:01	LRIKILCATYVK	12	Consensus	2.39	-	1.97
HLA-DRB1*15:01	LRIKILCATYVK	12	Consensus	3.26	-	11.16
HLA-DPA1*01:03 /DPB1*02:01	LRIKILCATYVKV	13	Consensus	8.42	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	LRIKILCATYVKV	13	NetMHCIIpan	4.21	377.53	17.41
HLA-DRB1*01:01	LRIKILCATYVKV	13	Consensus	2.03	-	7.54

HLA-DRB1*07:01	LRIKILCATYVKV	13	Consensus	4.68	-	12.21
HLA-DRB1*08:02	LRIKILCATYVKV	13	Consensus	6.24	-	0.68
HLA-DRB1*12:01	LRIKILCATYVKV	13	Consensus	2.11	-	1.97
HLA-DRB1*13:02	LRIKILCATYVKV	13	Consensus	6.71	-	4.60
HLA-DRB1*15:01	LRIKILCATYVKV	13	Consensus	2.03	-	11.16
HLA-DRB3*02:02	LRIKILCATYVKV	13	NetMHCIIpan	7.8	679.95	16.40
HLA-DRB4*01:01	LRIKILCATYVKV	13	Consensus	7.48	-	28.00
HLA-DRB5*01:01	LRIKILCATYVKV	13	Consensus	7.33	-	16.10
HLA-DPA1*01:03 /DPB1*02:01	LRIKILCATYVKVN	14	Consensus	7.11	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	LRIKILCATYVKVN	14	NetMHCIIpan	3.77	286.69	17.41
HLA-DRB1*01:01	LRIKILCATYVKVN	14	Consensus	1.94	-	7.54
HLA-DRB1*04:05	LRIKILCATYVKVN	14	Consensus	8.51	-	1.16
HLA-DRB1*07:01	LRIKILCATYVKVN	14	Consensus	4.63	-	12.21
HLA-DRB1*08:02	LRIKILCATYVKVN	14	Consensus	5.92	-	0.68
HLA-DRB1*12:01	LRIKILCATYVKVN	14	Consensus	1.88	-	1.97
HLA-DRB1*13:02	LRIKILCATYVKVN	14	Consensus	5.38	-	4.60
HLA-DRB1*15:01	LRIKILCATYVKVN	14	Consensus	2.15	-	11.16
HLA-DRB3*02:02	LRIKILCATYVKVN	14	NetMHCIIpan	7	533.12	16.40
HLA-DRB4*01:01	LRIKILCATYVKVN	14	Consensus	7.43	-	28.00
HLA-DRB5*01:01	LRIKILCATYVKVN	14	Consensus	6.35	-	16.10
HLA-DPA1*01:03 /DPB1*02:01	LRIKILCATYVKVNI	15	Consensus	8	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	LRIKILCATYVKVNI	15	NetMHCIIpan	3.5	190.24	17.41

HLA-DRB1*01:01	LRIKILCATYVKVNI	15	Consensus	2.2	-	7.54
HLA-DRB1*07:01	LRIKILCATYVKVNI	15	Consensus	5.6	-	12.21
HLA-DRB1*08:02	LRIKILCATYVKVNI	15	Consensus	7.1	-	0.68
HLA-DRB1*12:01	LRIKILCATYVKVNI	15	Consensus	2.4	-	1.97
HLA-DRB1*13:02	LRIKILCATYVKVNI	15	Consensus	5.7	-	4.60
HLA-DRB1*15:01	LRIKILCATYVKVNI	15	Consensus	3.1	-	11.16
HLA-DRB3*02:02	LRIKILCATYVKVNI	15	NetMHCIIpan	9.4	579.2	16.40
HLA-DRB4*01:01	LRIKILCATYVKVNI	15	Consensus	8.2	-	28.00
HLA-DRB5*01:01	LRIKILCATYVKVNI	15	Consensus	7.3	-	16.10
HLA-DPA1*01:03 /DPB1*04:01	LRIKILCATYVKVNIR	16	NetMHCIIpan	5.19	195.64	17.41
HLA-DPA1*02:01 /DPB1*14:01	LRIKILCATYVKVNIR	16	NetMHCIIpan	7.27	830.02	11.59
HLA-DRB1*01:01	LRIKILCATYVKVNIR	16	Consensus	3.69	-	7.54
HLA-DRB1*07:01	LRIKILCATYVKVNIR	16	Consensus	8.89	-	12.21
HLA-DRB1*08:02	LRIKILCATYVKVNIR	16	Consensus	8.89	-	0.68
HLA-DRB1*12:01	LRIKILCATYVKVNIR	16	Consensus	3.81	-	1.97
HLA-DRB1*13:02	LRIKILCATYVKVNIR	16	Consensus	7.5	-	4.60
HLA-DRB1*15:01	LRIKILCATYVKVNIR	16	Consensus	5.66	-	11.16
HLA-DRB3*02:02	LRIKILCATYVKVNIR	16	NetMHCIIpan	13.85	758.64	16.40
HLA-DPA1*01:03 /DPB1*04:01	LRIKILCATYVKVNIRD	17	NetMHCIIpan	10.39	228.72	17.41
HLA-DPA1*02:01 /DPB1*14:01	LRIKILCATYVKVNIRD	17	NetMHCIIpan	16.01	905.64	11.59
HLA-DRB1*01:01	LRIKILCATYVKVNIRD	17	Consensus	6.3	-	7.54
HLA-DRB1*12:01	LRIKILCATYVKVNIRD	17	Consensus	7.15	-	1.97

HLA-DPA1*01:03 /DPB1*04:01	LRIKILCATYVKVNIRDI	18	NetMHCIIpan	21.01	234.8	17.41
HLA-DPA1*02:01 /DPB1*14:01	LRIKILCATYVKVNIRDI	18	NetMHCIIpan	32.56	884.3	11.59
HLA-DRB1*09:01	LRIKILCATYVKVNIRDI	18	Consensus	2.9	-	1.68
HLA-DRB1*08:02	LWVINSALRIKI	12	Consensus	5.34	-	0.68
HLA-DRB1*11:01	LWVINSALRIKI	12	Consensus	6.82	-	4.25
HLA-DRB1*08:02	LWVINSALRIKIL	13	Consensus	4.05	-	0.68
HLA-DRB1*11:01	LWVINSALRIKIL	13	Consensus	4.83	-	4.25
HLA-DRB1*03:01	LWVINSALRIKILC	14	Consensus	9.15	-	9.82
HLA-DRB1*08:02	LWVINSALRIKILC	14	Consensus	3.98	-	0.68
HLA-DRB1*11:01	LWVINSALRIKILC	14	Consensus	4.41	-	4.25
HLA-DRB1*15:01	LWVINSALRIKILC	14	Consensus	8.94	-	11.16
HLA-DRB1*08:02	LWVINSALRIKILCA	15	Consensus	4.2	-	0.68
HLA-DRB1*11:01	LWVINSALRIKILCA	15	Consensus	4.9	-	4.25
HLA-DRB1*15:01	LWVINSALRIKILCA	15	Consensus	9.6	-	11.16
HLA-DRB1*08:02	LWVINSALRIKILCAT	16	Consensus	1.96	-	0.68
HLA-DRB1*11:01	LWVINSALRIKILCAT	16	Consensus	7.04	-	4.25
HLA-DRB1*15:01	LWVINSALRIKILCAT	16	Consensus	4.85	-	11.16
HLA-DRB3*01:01	LWVINSALRIKILCAT	16	Consensus	3.23	-	18.00
HLA-DRB5*01:01	LWVINSALRIKILCAT	16	Consensus	6.81	-	16.10
HLA-DRB1*08:02	LWVINSALRIKILCATY	17	Consensus	2.9	-	0.68
HLA-DRB1*15:01	LWVINSALRIKILCATY	17	Consensus	8.35	-	11.16
HLA-DRB3*01:01	LWVINSALRIKILCATY	17	Consensus	5.45	-	18.00

HLA-DRB1*01:01	LWVINSALRIKILCATYV	18	Consensus	6.22	-	7.54
HLA-DRB1*08:02	LWVINSALRIKILCATYV	18	Consensus	3.85	-	0.68
HLA-DRB1*15:01	LWVINSALRIKILCATYV	18	Consensus	9.77	-	11.16
HLA-DRB1*08:02	MPSYSRRISTATPY	14	Consensus	9.05	-	0.68
HLA-DRB1*11:01	NIRDIDKIYVRTGI	14	Consensus	8.4	-	4.25
HLA-DRB1*01:01	NSALRIKILCATYV	14	Consensus	1.94	-	7.54
HLA-DRB1*08:02	NSALRIKILCATYV	14	Consensus	3.55	-	0.68
HLA-DRB1*13:02	NSALRIKILCATYV	14	Consensus	7.75	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	NSALRIKILCATYVK	15	NetMHCIIpan	17	796.51	17.41
HLA-DQA1*01:02 /DQB1*06:02	NSALRIKILCATYVK	15	Consensus	5.1	-	10.40
HLA-DRB1*01:01	NSALRIKILCATYVK	15	Consensus	2	-	7.54
HLA-DRB1*04:05	NSALRIKILCATYVK	15	Consensus	8.9	-	1.16
HLA-DRB1*07:01	NSALRIKILCATYVK	15	Consensus	6	-	12.21
HLA-DRB1*08:02	NSALRIKILCATYVK	15	Consensus	4.1	-	0.68
HLA-DRB1*12:01	NSALRIKILCATYVK	15	Consensus	2.05	-	1.97
HLA-DRB1*13:02	NSALRIKILCATYVK	15	Consensus	8.7	-	4.60
HLA-DRB1*15:01	NSALRIKILCATYVK	15	Consensus	3.8	-	11.16
HLA-DRB4*01:01	NSALRIKILCATYVK	15	Consensus	4.6	-	28.00
HLA-DRB5*01:01	NSALRIKILCATYVK	15	Consensus	7.6	-	16.10
HLA-DPA1*01:03 /DPB1*04:01	NSALRIKILCATYVKV	16	NetMHCIIpan	6.46	227.42	17.41
HLA-DPA1*02:01 /DPB1*14:01	NSALRIKILCATYVKV	16	NetMHCIIpan	6.93	812.64	11.59
HLA-DQA1*01:02 /DQB1*06:02	NSALRIKILCATYVKV	16	Consensus	9.12	-	10.40

HLA-DRB1*01:01	NSALRIKILCATYVKV	16	Consensus	3.46	-	7.54
HLA-DRB1*07:01	NSALRIKILCATYVKV	16	Consensus	7.04	-	12.21
HLA-DRB1*08:02	NSALRIKILCATYVKV	16	Consensus	7.73	-	0.68
HLA-DRB1*12:01	NSALRIKILCATYVKV	16	Consensus	3.23	-	1.97
HLA-DRB1*13:02	NSALRIKILCATYVKV	16	Consensus	7.5	-	4.60
HLA-DRB1*15:01	NSALRIKILCATYVKV	16	Consensus	4.73	-	11.16
HLA-DRB3*02:02	NSALRIKILCATYVKV	16	NetMHCIIpan	17.31	927.44	16.40
HLA-DRB4*01:01	NSALRIKILCATYVKV	16	Consensus	6.81	-	28.00
HLA-DPA1*01:03 /DPB1*04:01	NSALRIKILCATYVKVN	17	NetMHCIIpan	11.75	249.33	17.41
HLA-DPA1*02:01 /DPB1*14:01	NSALRIKILCATYVKVN	17	NetMHCIIpan	12.77	788.03	11.59
HLA-DRB1*01:01	NSALRIKILCATYVKVN	17	Consensus	5.96	-	7.54
HLA-DRB1*12:01	NSALRIKILCATYVKVN	17	Consensus	5.19	-	1.97
HLA-DRB1*15:01	NSALRIKILCATYVKVN	17	Consensus	8.86	-	11.16
HLA-DPA1*01:03 /DPB1*04:01	NSALRIKILCATYVKVNI	18	NetMHCIIpan	19.53	224.99	17.41
HLA-DPA1*02:01 /DPB1*14:01	NSALRIKILCATYVKVNI	18	NetMHCIIpan	24.86	756.1	11.59
HLA-DRB1*04:01	PYMNGETSTKSL	12	Consensus	9.49	-	6.37
HLA-DRB1*04:01	PYMNGETSTKSLW	13	Consensus	8.11	-	6.37
HLA-DRB1*04:01	PYMNGETSTKSLWV	14	Consensus	7.11	-	6.37
HLA-DRB1*04:01	PYMNGETSTKSLWVI	15	Consensus	8.6	-	6.37
HLA-DRB1*04:01	PYMNGETSTKSLWVIN	16	Consensus	6.46	-	6.37
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKV	12	NetMHCIIpan	5.63	514.7	17.41
HLA-DRB1*01:01	RIKILCATYVKV	12	Consensus	5.04	-	7.54

HLA-DRB1*12:01	RIKILCATYVKV	12	Consensus	6.82	-	1.97
HLA-DRB1*15:01	RIKILCATYVKV	12	Consensus	3.56	-	11.16
HLA-DRB3*02:02	RIKILCATYVKV	12	NetMHCIIpan	10.68	976.07	16.40
HLA-DPA1*01:03 /DPB1*02:01	RIKILCATYVKVN	13	Consensus	8.89	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKVN	13	NetMHCIIpan	4.68	407.54	17.41
HLA-DRB1*01:01	RIKILCATYVKVN	13	Consensus	4.21	-	7.54
HLA-DRB1*07:01	RIKILCATYVKVN	13	Consensus	7.95	-	12.21
HLA-DRB1*12:01	RIKILCATYVKVN	13	Consensus	4.83	-	1.97
HLA-DRB1*15:01	RIKILCATYVKVN	13	Consensus	2.81	-	11.16
HLA-DRB3*02:02	RIKILCATYVKVN	13	NetMHCIIpan	8.26	710.19	16.40
HLA-DPA1*01:03 /DPB1*02:01	RIKILCATYVKVNI	14	Consensus	7.43	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKVNI	14	NetMHCIIpan	3.23	248.03	17.41
HLA-DRB1*01:01	RIKILCATYVKVNI	14	Consensus	5.28	-	7.54
HLA-DRB1*07:01	RIKILCATYVKVNI	14	Consensus	7.11	-	12.21
HLA-DRB1*12:01	RIKILCATYVKVNI	14	Consensus	4.36	-	1.97
HLA-DRB1*15:01	RIKILCATYVKVNI	14	Consensus	2.91	-	11.16
HLA-DRB3*02:02	RIKILCATYVKVNI	14	NetMHCIIpan	7.86	593.17	16.40
HLA-DPA1*01:03 /DPB1*02:01	RIKILCATYVKVNIR	15	Consensus	8.3	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKVNIR	15	NetMHCIIpan	3.8	203.42	17.41
HLA-DRB1*01:01	RIKILCATYVKVNIR	15	Consensus	7.5	-	7.54
HLA-DRB1*07:01	RIKILCATYVKVNIR	15	Consensus	7.9	-	12.21
HLA-DRB1*12:01	RIKILCATYVKVNIR	15	Consensus	5.6	-	1.97

HLA-DRB1*15:01	RIKILCATYVKVNIR	15	Consensus	4.4	-	11.16
HLA-DRB3*02:02	RIKILCATYVKVNIR	15	NetMHCIIpan	11	650.26	16.40
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKVNIRD	16	NetMHCIIpan	6.23	222.45	17.41
HLA-DPA1*02:01 /DPB1*14:01	RIKILCATYVKVNIRD	16	NetMHCIIpan	9.47	979.06	11.59
HLA-DRB1*01:01	RIKILCATYVKVNIRD	16	Consensus	4.16	-	7.54
HLA-DRB1*07:01	RIKILCATYVKVNIRD	16	Consensus	9.7	-	12.21
HLA-DRB1*12:01	RIKILCATYVKVNIRD	16	Consensus	6.75	-	1.97
HLA-DRB1*15:01	RIKILCATYVKVNIRD	16	Consensus	7.96	-	11.16
HLA-DRB3*02:02	RIKILCATYVKVNIRD	16	NetMHCIIpan	17.31	962.33	16.40
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKVNIRDI	17	NetMHCIIpan	11.24	240.54	17.41
HLA-DPA1*02:01 /DPB1*14:01	RIKILCATYVKVNIRDI	17	NetMHCIIpan	18.74	986.48	11.59
HLA-DRB1*01:01	RIKILCATYVKVNIRDI	17	Consensus	7.15	-	7.54
HLA-DRB1*07:01	RIKILCATYVKVNIRDI	17	Consensus	6.98	-	12.21
HLA-DRB1*09:01	RIKILCATYVKVNIRDI	17	Consensus	1.53	-	1.68
HLA-DRB1*13:02	RIKILCATYVKVNIRDI	17	Consensus	7.83	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	RIKILCATYVKVNIRDID	18	NetMHCIIpan	25.16	268.14	17.41
HLA-DRB1*09:01	RIKILCATYVKVNIRDID	18	Consensus	3.26	-	1.68
HLA-DRB1*01:01	SALRIKILCATYV	13	Consensus	2.03	-	7.54
HLA-DRB1*08:02	SALRIKILCATYV	13	Consensus	4.05	-	0.68
HLA-DRB1*13:02	SALRIKILCATYV	13	Consensus	8.73	-	4.60
HLA-DPA1*01:03 /DPB1*04:01	SALRIKILCATYVK	14	NetMHCIIpan	14	978.7	17.41
HLA-DRB1*01:01	SALRIKILCATYVK	14	Consensus	1.94	-	7.54

HLA-DRB1*04:05	SALRIKILCATYVK	14	Consensus	8.08	-	1.16
HLA-DRB1*07:01	SALRIKILCATYVK	14	Consensus	5.06	-	12.21
HLA-DRB1*08:02	SALRIKILCATYVK	14	Consensus	3.88	-	0.68
HLA-DRB1*12:01	SALRIKILCATYVK	14	Consensus	1.56	-	1.97
HLA-DRB1*13:02	SALRIKILCATYVK	14	Consensus	7.65	-	4.60
HLA-DRB1*15:01	SALRIKILCATYVK	14	Consensus	2.48	-	11.16
HLA-DRB3*02:02	SALRIKILCATYVK	14	NetMHCIIpan	11.84	877.8	16.40
HLA-DRB4*01:01	SALRIKILCATYVK	14	Consensus	5.71	-	28.00
HLA-DRB5*01:01	SALRIKILCATYVK	14	Consensus	6.46	-	16.10
HLA-DPA1*01:03 /DPB1*02:01	SALRIKILCATYVKV	15	Consensus	8.6	-	15.31
HLA-DPA1*01:03 /DPB1*04:01	SALRIKILCATYVKV	15	NetMHCIIpan	4.5	228.7	17.41
HLA-DPA1*02:01 /DPB1*14:01	SALRIKILCATYVKV	15	NetMHCIIpan	4.4	932.51	11.59
HLA-DRB1*01:01	SALRIKILCATYVKV	15	Consensus	2	-	7.54
HLA-DRB1*04:05	SALRIKILCATYVKV	15	Consensus	8.9	-	1.16
HLA-DRB1*07:01	SALRIKILCATYVKV	15	Consensus	4.9	-	12.21
HLA-DRB1*08:02	SALRIKILCATYVKV	15	Consensus	4.4	-	0.68
HLA-DRB1*12:01	SALRIKILCATYVKV	15	Consensus	1.8	-	1.97
HLA-DRB1*13:02	SALRIKILCATYVKV	15	Consensus	5.7	-	4.60
HLA-DRB1*15:01	SALRIKILCATYVKV	15	Consensus	2.6	-	11.16
HLA-DRB3*02:02	SALRIKILCATYVKV	15	NetMHCIIpan	11	639.82	16.40
HLA-DRB4*01:01	SALRIKILCATYVKV	15	Consensus	6.2	-	28.00
HLA-DRB5*01:01	SALRIKILCATYVKV	15	Consensus	7.1	-	16.10

HLA-DPA1*01:03 /DPB1*04:01	SALRIKILCATYVKVN	16	NetMHCIIpan	6.46	226.93	17.41
HLA-DPA1*02:01 /DPB1*14:01	SALRIKILCATYVKVN	16	NetMHCIIpan	6.58	792.9	11.59
HLA-DRB1*01:01	SALRIKILCATYVKVN	16	Consensus	3.35	-	7.54
HLA-DRB1*07:01	SALRIKILCATYVKVN	16	Consensus	7.73	-	12.21
HLA-DRB1*08:02	SALRIKILCATYVKVN	16	Consensus	7.62	-	0.68
HLA-DRB1*12:01	SALRIKILCATYVKVN	16	Consensus	2.89	-	1.97
HLA-DRB1*13:02	SALRIKILCATYVKVN	16	Consensus	7.5	-	4.60
HLA-DRB1*15:01	SALRIKILCATYVKVN	16	Consensus	4.5	-	11.16
HLA-DRB3*02:02	SALRIKILCATYVKVN	16	NetMHCIIpan	15.01	785.89	16.40
HLA-DRB4*01:01	SALRIKILCATYVKVN	16	Consensus	7.5	-	28.00
HLA-DPA1*01:03 /DPB1*04:01	SALRIKILCATYVKVNI	17	NetMHCIIpan	9.37	210.78	17.41
HLA-DPA1*02:01 /DPB1*14:01	SALRIKILCATYVKVNI	17	NetMHCIIpan	12.26	763.95	11.59
HLA-DRB1*01:01	SALRIKILCATYVKVNI	17	Consensus	5.79	-	7.54
HLA-DRB1*12:01	SALRIKILCATYVKVNI	17	Consensus	5.11	-	1.97
HLA-DRB1*15:01	SALRIKILCATYVKVNI	17	Consensus	8.86	-	11.16
HLA-DRB3*02:02	SALRIKILCATYVKVNI	17	NetMHCIIpan	23.85	935.3	16.40
HLA-DPA1*01:03 /DPB1*04:01	SALRIKILCATYVKVNIR	18	NetMHCIIpan	19.24	223.06	17.41
HLA-DPA1*02:01 /DPB1*14:01	SALRIKILCATYVKVNIR	18	NetMHCIIpan	23.09	711.22	11.59
HLA-DRB3*02:02	SALRIKILCATYVKVNIR	18	NetMHCIIpan	44.4	978.08	16.40
HLA-DRB1*01:01	SLWVINSALRIK	12	Consensus	8.9	-	7.54
HLA-DRB1*08:02	SLWVINSALRIK	12	Consensus	7.12	-	0.68
HLA-DRB1*15:01	SLWVINSALRIK	12	Consensus	8.9	-	11.16

HLA-DRB1*11:01	SLWVINSALRIKI	13	Consensus	4.52	-	4.25
HLA-DRB1*03:01	SLWVINSALRIKIL	14	Consensus	9.15	-	9.82
HLA-DRB1*11:01	SLWVINSALRIKIL	14	Consensus	3.66	-	4.25
HLA-DRB1*08:02	SLWVINSALRIKILC	15	Consensus	4.2	-	0.68
HLA-DRB1*11:01	SLWVINSALRIKILC	15	Consensus	4.3	-	4.25
HLA-DRB1*15:01	SLWVINSALRIKILC	15	Consensus	5.8	-	11.16
HLA-DRB1*08:02	SLWVINSALRIKILCA	16	Consensus	3.58	-	0.68
HLA-DRB1*11:01	SLWVINSALRIKILCA	16	Consensus	6.93	-	4.25
HLA-DRB1*15:01	SLWVINSALRIKILCA	16	Consensus	4.85	-	11.16
HLA-DRB1*08:02	SLWVINSALRIKILCAT	17	Consensus	2.9	-	0.68
HLA-DRB1*15:01	SLWVINSALRIKILCAT	17	Consensus	8.18	-	11.16
HLA-DRB3*01:01	SLWVINSALRIKILCAT	17	Consensus	5.28	-	18.00
HLA-DRB1*08:02	SLWVINSALRIKILCATY	18	Consensus	5.33	-	0.68
HLA-DRB3*01:01	SLWVINSALRIKILCATY	18	Consensus	9.77	-	18.00
HLA-DRB1*04:01	STATPYMNGETSTKS	15	Consensus	4.7	-	6.37
HLA-DRB1*04:01	STATPYMNGETSTKSL	16	Consensus	6.35	-	6.37
HLA-DRB1*01:01	STKSLWVINSALRI	14	Consensus	4.52	-	7.54
HLA-DRB1*03:01	STKSLWVINSALRI	14	Consensus	9.15	-	9.82
HLA-DRB1*11:01	STKSLWVINSALRIKI	16	Consensus	7.5	-	4.25
HLA-DRB1*08:02	STKSLWVINSALRIKIL	17	Consensus	5.96	-	0.68
HLA-DRB1*15:01	STKSLWVINSALRIKIL	17	Consensus	7.83	-	11.16
HLA-DRB3*01:01	STKSLWVINSALRIKILC	18	Consensus	9.47	-	18.00

HLA-DRB1*04:01	TATPYMNGETSTKS	14	Consensus	4.52	-	6.37
HLA-DRB1*04:01	TATPYMNGETSTKSL	15	Consensus	4.7	-	6.37
HLA-DRB1*04:01	TATPYMNGETSTKSLW	16	Consensus	6.35	-	6.37
HLA-DRB1*01:01	TKSLWVINSALRI	13	Consensus	5.61	-	7.54
HLA-DRB1*03:01	TKSLWVINSALRIK	14	Consensus	9.15	-	9.82
HLA-DRB1*11:01	TKSLWVINSALRIKI	15	Consensus	4.5	-	4.25
HLA-DRB1*11:01	TKSLWVINSALRIKIL	16	Consensus	6.93	-	4.25
HLA-DRB1*08:02	TKSLWVINSALRIKILC	17	Consensus	5.96	-	0.68
HLA-DRB1*15:01	TKSLWVINSALRIKILC	17	Consensus	7.83	-	11.16
HLA-DRB3*01:01	TKSLWVINSALRIKILCA	18	Consensus	9.47	-	18.00
HLA-DRB1*08:02	TMPSYSRRISTATP	14	Consensus	8.94	-	0.68
HLA-DRB1*04:01	TPYMNGETSTKS	12	Consensus	8.9	-	6.37
HLA-DRB1*04:01	TPYMNGETSTKSL	13	Consensus	5.61	-	6.37
HLA-DRB1*04:01	TPYMNGETSTKSLW	14	Consensus	4.52	-	6.37
HLA-DRB1*04:01	TPYMNGETSTKSLWV	15	Consensus	4.7	-	6.37
HLA-DRB1*04:01	TPYMNGETSTKSLWVI	16	Consensus	6.35	-	6.37
HLA-DRB1*01:01	TSTKSLWVINSALRI	15	Consensus	4.8	-	7.54
HLA-DRB1*08:02	TSTKSLWVINSALRI	15	Consensus	2.7	-	0.68
HLA-DRB1*08:02	TSTKSLWVINSALRIK	16	Consensus	3.58	-	0.68
HLA-DRB1*15:01	TSTKSLWVINSALRIK	16	Consensus	5.19	-	11.16
HLA-DRB1*08:02	TSTKSLWVINSALRIKI	17	Consensus	5.96	-	0.68
HLA-DRB1*15:01	TSTKSLWVINSALRIKI	17	Consensus	8.18	-	11.16

HLA-DRB3*01:01	TSTKSLWVINSALRIKIL	18	Consensus	9.47	-	18.00
HLA-DRB1*01:01	VINSALRIKILCATYV	16	Consensus	3.69	-	7.54
HLA-DRB1*08:02	VINSALRIKILCATYV	16	Consensus	6.46	-	0.68
HLA-DPA1*01:03 /DPB1*04:01	VINSALRIKILCATYVK	17	NetMHCIIpan	35.77	669.67	17.41
HLA-DQA1*01:02 /DQB1*06:02	VINSALRIKILCATYVK	17	Consensus	4.26	-	10.40
HLA-DRB1*01:01	VINSALRIKILCATYVK	17	Consensus	6.13	-	7.54
HLA-DRB1*12:01	VINSALRIKILCATYVK	17	Consensus	4.09	-	1.97
HLA-DPA1*01:03 /DPB1*04:01	VINSALRIKILCATYVKV	18	NetMHCIIpan	23.09	250.89	17.41
HLA-DPA1*02:01 /DPB1*14:01	VINSALRIKILCATYVKV	18	NetMHCIIpan	24.86	756.7	11.59
HLA-DQA1*01:02 /DQB1*06:02	VINSALRIKILCATYVKV	18	Consensus	9.77	-	10.40
HLA-DRB1*12:01	VINSALRIKILCATYVKV	18	Consensus	7.55	-	1.97
HLA-DRB1*03:01	VKVNIRDIDKIYVR	14	Consensus	8.18	-	9.82
HLA-DRB1*03:01	VKVNIRDIDKIYVRT	15	Consensus	9.3	-	9.82
HLA-DRB1*11:01	VNIRDIDKIYVRTG	14	Consensus	8.08	-	4.25
HLA-DRB1*11:01	VNIRDIDKIYVRTGI	15	Consensus	8.7	-	4.25
HLA-DRB1*11:01	WVINSALRIKIL	12	Consensus	6.82	-	4.25
HLA-DRB3*01:01	WVINSALRIKIL	12	Consensus	9.19	-	18.00
HLA-DRB1*11:01	WVINSALRIKILC	13	Consensus	5.46	-	4.25
HLA-DRB3*01:01	WVINSALRIKILC	13	Consensus	6.39	-	18.00
HLA-DRB1*01:01	WVINSALRIKILCA	14	Consensus	9.91	-	7.54
HLA-DRB1*03:01	WVINSALRIKILCA	14	Consensus	9.15	-	9.82
HLA-DRB1*11:01	WVINSALRIKILCA	14	Consensus	4.52	-	4.25

	HLA-DRB3*01:01	WVINSALRIKILCA	14	Consensus	5.81	-	18.00
	HLA-DRB1*11:01	WVINSALRIKILCAT	15	Consensus	5.2	-	4.25
	HLA-DRB3*01:01	WVINSALRIKILCAT	15	Consensus	6.8	-	18.00
	HLA-DRB1*11:01	WVINSALRIKILCATY	16	Consensus	7.5	-	4.25
	HLA-DRB3*01:01	WVINSALRIKILCATY	16	Consensus	3.35	-	18.00
	HLA-DRB1*01:01	WVINSALRIKILCATYV	17	Consensus	3.41	-	7.54
	HLA-DRB1*11:01	WVINSALRIKILCATYV	17	Consensus	6.13	-	4.25
	HLA-DRB1*15:01	WVINSALRIKILCATYV	17	Consensus	5.11	-	11.16
	HLA-DRB3*01:01	WVINSALRIKILCATYV	17	Consensus	5.62	-	18.00
	HLA-DPA1*01:03 /DPB1*04:01	WVINSALRIKILCATYVK	18	NetMHCIIpan	41.44	397.76	17.41
	HLA-DPA1*02:01 /DPB1*14:01	WVINSALRIKILCATYVK	18	NetMHCIIpan	26.05	781.41	11.59
	HLA-DQA1*01:02 /DQB1*06:02	WVINSALRIKILCATYVK	18	Consensus	7.7	-	10.40
	HLA-DRB1*01:01	WVINSALRIKILCATYVK	18	Consensus	6.22	-	7.54
	HLA-DRB1*12:01	WVINSALRIKILCATYVK	18	Consensus	3.66	-	1.97
	HLA-DRB1*13:02	WVINSALRIKILCATYVK	18	Consensus	2.46	-	4.60
	HLA-DRB1*15:01	WVINSALRIKILCATYVK	18	Consensus	9.77	-	11.16
	HLA-DRB3*02:02	WVINSALRIKILCATYVK	18	NetMHCIIpan	6.51	146.81	16.40
	HLA-DRB1*04:01	YMNGETSTKSLWVINS	16	Consensus	6.35	-	6.37
	HLA-DRB1*03:01	YVKVNIRDIDKIYVR	15	Consensus	9.4	-	9.82
TP53 R175H	HLA-DQA1*01:02 /DQB1*06:02	KQSQHMTEVVRHCP	14	Consensus	8.2	-	10.40
	HLA-DQA1*01:02 /DQB1*06:02	KQSQHMTEVVRHCPH	15	Consensus	8	-	10.40
	HLA-DQA1*01:02 /DQB1*06:02	QSQHMTEVVRHCPH	14	Consensus	7.4	-	10.40

Supplementary table 4 Sample ID of samples with known germline *BRCA1* mutations reported by previous studies

Nik-Zanial et al. 2016	Nones et al. 2019	Inagaki-Kawata et al. 2020
PD24202a	FBC108061	TCGA-D8-A1XK
PD8621a	FBC110004	TCGA-D8-A1XQ
PD13296a	FBC110062	TCGA-AR-A24Q
PD24337a	FBC112021	TCGA-AO-A124
PD9702a	FBC208006	TCGA-A7-A4SE
PD6406a	FBC712007	TCGA-D8-A147
PD9004a	FBC406015	TCGA-C8-A12K
PD3905a	FBC016026	TCGA-E2-A14N
PD24186a	FBC020030	TCGA-E9-A244
PD4005a	FBC061126	TCGA-E9-A22G
PD13771a	FBC020187	TCGA-A1-A0SH
PD13297a	FBC070197	TCGA-E9-A22E
PD5935a	FBC100739	TCGA-E2-A14Z
PD11327a	FBC020675	TCGA-EW-A1P4
PD10014a	FBC070890	TCGA-E2-A1IJ
PD3890a	FBC060097	TCGA-BH-A0BL
PD5930a	FBC060467	KU045
PD8980a	FBC020034	KU016
PD14442a	FBC070205	KU014
PD4006a	FBC060031	KU009
PD13299a	FBC020091	KU085
PD4107a	FBC030130	
PD23562a	FBC061699	
PD5945a	FBC071015	
PD22355a	FBC080607	
PD23574a	FBC090326	
PD23578a		
PD6413a		
PD6731a2		
PD5948a		
PD13627a		

Supplementary Table 5 *BRCA1*-positive and -negative sample ID from 3 databases

TCGA: *BRCA1*- positive

Sample ID	DNA Change(BRCA1 mutation)	BRCA1 mutation type	ACMG prediction	GRCh
TCGA-BH-A0WA	chr17:g.43071239C>T	Splice Acceptor BRCA1 X1580_splice	pathogenic	38
TCGA-A1-A0SI	chr17:g.43124016C>T	Splice Donor BRCA1 X27_splice	pathogenic	38
TCGA-A2-A25B	chr17:g.43093373C>A	Stop Gained BRCA1 E720*	pathogenic	38
TCGA-A1-A0SH	chr17:g.43092731G>A	Stop Gained BRCA1 Q934*	pathogenic	38
TCGA-A7-A6VW	chr17:g.43092822delA	Frameshift BRCA1 C903Wfs*97	pathogenic	38
TCGA-A7-A26H	chr17:g.43093467delTGTC	Frameshift BRCA1 T688Vfs*12	pathogenic	38
TCGA-LL-A8F5	chr17:g.43082539G>A	Stop Gained BRCA1 Q1408*	pathogenic	38
TCGA-A8-A06X	chr17:g.43094717C>A	Stop Gained BRCA1 E272*	pathogenic	38
TCGA-B6-A0X1	chr17:g.43124030delC	Frameshift BRCA1 E23Sfs*8	pathogenic	38
05BR052	chr17:g.43092073delA	Frameshift BRCA1 L1153Rfs*2	pathogenic	38
TCGA-E9-A1NC	chr17:g.43104148G>A	Stop Gained BRCA1 Q139*	pathogenic	38
TCGA-D8-A27M	chr17:g.43071073delG	Frameshift BRCA1 P1635Qfs*19	likely pathogenic	38
TCGA-AN-A0XU	chr17:g.43049164C>A	Missense BRCA1 G1809V	pathogenic	38

ICGC: *BRCA1*- positive

Sample ID	DNA change (BRCA1 mutation)	ACMG prediction	GRCh
DO225079	chr17:g.41234451G>A	Pathogenic	37
DO224917	chr17:g.41246005C>A	Pathogenic	37
DO225334	chr17:g.41247865->T	Likely Pathogenic	37
DO225328	chr17:g.41215381T>C	Likely Pathogenic	37
DO218669	chr17:g.41209130T>A	Pathogenic	37
DO1261	chr17:g.41244748G>A	Pathogenic	37
DO1712	chr17:g.41201181C>A	Pathogenic	37
DO2020	chr17:g.41276033C>T	Pathogenic	37
DO3916	chr17:g.41244185->T	Likely Pathogenic	37
DO50068	chr17:g.41234556G>A	Pathogenic	37
DO51226	chr17:g.41243563C>A	Pathogenic	37
DO5074	chr17:g.41246734C>A	Pathogenic	37
DO5130	chr17:g.41199695T>A	Likely Pathogenic	37
DO2897	chr17:g.41223256C>T	Pathogenic	37
DO2706	chr17:g.41245390C>A	Pathogenic	37

COSMIC: *BRCA1*- positive

Sample ID	AA change (BRCA1 mutation)	CDS Mutation	ACMG prediction	GRCh
1509149	p.E515*	c.1543G>T	pathogenic	38
1527353	p.D1760V	c.5279A>T	pathogenic	38
1649378	p.R1443*	c.4327C>T	pathogenic	38
1660108	p.?	c.135-1215C>G	pathogenic	38
1768176	p.F1793Lfs*29	c.5356_5378dup	pathogenic	38
1779256	p.Q934*	c.2800C>T	pathogenic	38
1779260	p.?	c.80+1G>A	pathogenic	38
1779502	p.N1121Kfs*12	c.3362dup	likely pathogenic	38
1779649	p.?	c.4739-1G>A	pathogenic	38
1899647	p.E720*	c.2158G>T	pathogenic	38
1899672	p.E272*	c.814G>T	pathogenic	38
1899768	p.G1809V	c.5426G>T	pathogenic	38
1899917	p.Q1832L	c.5495A>T	likely pathogenic	38
1900097	p.P1635Qfs*19	c.4904del	likely pathogenic	38
2199791	p.Q1742R	c.5225A>G	likely pathogenic	38
2213140	p.A224Gfs*4	c.668dup	likely pathogenic	38
2262906	p.Q1408*	c.4222C>T	pathogenic	38
2318501	p.S1817Lfs*34	c.5448_5449insC	likely pathogenic	38
2339544	p.E1329*	c.3985G>T	pathogenic	38
2579117	p.D1526Mfs*43	c.4575del	likely pathogenic	38
2657324	p.E1419*	c.4255G>T	pathogenic	38
2662750	p.R1747Kfs*5	c.5240_5241del	pathogenic	38
2673932	p.C61Y	c.182G>A	pathogenic	38
2697837	p.R1610C	c.4828C>T	pathogenic	38
2697863	p.W1836*	c.5507G>A	pathogenic	38
2724995	p.R71Kfs*10	c.211dup	pathogenic	38
2725854	p.G911Efs*89	c.2732del	likely pathogenic	38
2726190	p.K1745*	c.5233A>T	pathogenic	38
2767653	p.E1250*	c.3748G>T	pathogenic	38
2767723	p.E1752Q	c.5254G>C	likely pathogenic	38
2768049	p.G928Afs*72	c.2783del	pathogenic	38
2768180	p.R1856Q	c.5567G>A	likely pathogenic	38
2768268	p.K608Ifs*3	c.1823_1826del	pathogenic	38
2768429	p.N1355Kfs*10	c.4065_4068del	pathogenic	38
2768438	p.P1635Qfs*19	c.4904del	likely pathogenic	38
2768457	p.G948Efs*52	c.2838del	likely pathogenic	38
2768460	p.Y655Vfs*18	c.1961dup	pathogenic	38
2768485	p.L1086Dfs*2	c.3254_3255dup	pathogenic	38
2768525	p.K339Rfs*2	c.1016del	pathogenic	38

2768553	p.C1372Efs*2	c.4113_4117del	pathogenic	38
2768554	p.N714Kfs*4	c.2141dup	likely pathogenic	38
2768560	p.H437*	c.1308_1309del	likely pathogenic	38
2768689	p.N1029Kfs*3	c.3087_3088del	likely pathogenic	38
2768761	p.K894Tfs*8	c.2681_2682del	pathogenic	38
2768773	p.V340Gfs*6	c.1016dup	pathogenic	38
2768791	p.Q169*	c.505C>T	pathogenic	38
2768816	p.Y1584Tfs*38	c.4750del	likely pathogenic	38
2768819	p.M1804T	c.5411T>C	likely pathogenic	38
2768830	p.W372Yfs*5	c.1115_1116del	likely pathogenic	38
2768838	p.Q172Nfs*62	c.514del	pathogenic	38
2768840	p.R1443*	c.4327C>T	pathogenic	38
2768848	p.C1718R	c.5152T>C	pathogenic	38
2768851	p.E453Rfs*22	c.1357del	likely pathogenic	38
2768862	p.R1203*	c.3607C>T	pathogenic	38
2768869	p.H1284Tfs*23	c.3850del	likely pathogenic	38
2768880	p.Q1395*	c.4183C>T	pathogenic	38
2802997	p.Q12_V14delinsH	c.36_41del	likely pathogenic	38
2810731	p.R1856*	c.5566C>T	pathogenic	38
2810741	p.E1115*	c.3342_3345del	pathogenic	38
2823388	p.T1249P	c.3745A>C	pathogenic	38
2823406	p.E23Vfs*17	c.68_69del	pathogenic	38
2823407	p.Q1777Pfs*74	c.5329dup	pathogenic	38
2823443	p.E881*	c.2641G>T	pathogenic	38
2823472	p.E1282Afs*26	c.3844_3845insCG	likely pathogenic	38
2823478	p.Q1832R	c.5495A>G	pathogenic	38
2830181	p.R71Kfs*10	c.211dup	pathogenic	38

TCGA: *BRCA1*- negative

Sample ID				
TCGA-A8-A0AD	TCGA-B6-A0WV	TCGA-E2-A155	TCGA-C8-A26V	TCGA-B6-A0IN
TCGA-B6-A0RV	TCGA-C8-A12L	TCGA-AR-A250	TCGA-A8-A09D	TCGA-EW-A1OX
TCGA-AC-A23H	TCGA-AN-A0FW	TCGA-E9-A228	TCGA-S3-AA14	TCGA-EW-A2FV
TCGA-A8-A08L	TCGA-D8-A1X9	TCGA-OL-A5RZ	TCGA-A7-A13D	TCGA-LL-A6FP
TCGA-A8-A09I	TCGA-B6-A0IO	TCGA-C8-A275	TCGA-E9-A226	TCGA-AC-A2B8
TCGA-A2-A0EV	TCGA-BH-A0B1	TCGA-EW-A1OV	TCGA-BH-A1EV	TCGA-BH-A42T
TCGA-AR-A1AP	TCGA-BH-A0H7	TCGA-C8-A1HN	TCGA-A8-A085	TCGA-D8-A27G
TCGA-BH-A1F0	TCGA-C8-A135	TCGA-BH-A0BF	TCGA-OL-A6VO	TCGA-LQ-A4E4
TCGA-A7-A13G	TCGA-E2-A109	TCGA-EW-A1OZ	TCGA-AO-A12C	TCGA-AC-A2FB
TCGA-E2-A14W	TCGA-A2-A0YG	TCGA-BH-A0AW	TCGA-EW-A2FS	TCGA-A2-A0SY
TCGA-BH-A203	TCGA-EW-A1OY	TCGA-AN-A0FY	TCGA-E2-A1LB	TCGA-A8-A09X

TCGA-A1-A0SM	TCGA-B6-A0IK	TCGA-C8-A138	TCGA-E2-A1L7	TCGA-EW-A1J3
TCGA-BH-A0BP	TCGA-BH-A0C0	TCGA-A7-A4SF	TCGA-E9-A1RB	TCGA-EW-A6SC
TCGA-A8-A090	TCGA-D8-A140	TCGA-A2-A0EO	TCGA-A1-A0SJ	TCGA-D8-A27T
TCGA-AC-A5XU	TCGA-D8-A1JG	TCGA-A7-A2KD	TCGA-EW-A1J1	TCGA-A7-A426
TCGA-LD-A9QF	TCGA-BH-A0DX	TCGA-E2-A14T	TCGA-A7-A0D9	TCGA-AC-A6IX
TCGA-A2-A0CU	TCGA-AN-A0AT	TCGA-C8-A130	TCGA-C8-A1HO	TCGA-A2-A4RW
TCGA-BH-A0BW	TCGA-B6-A0I9	TCGA-AN-A04C	TCGA-AO-A03L	TCGA-B6-A0IE
TCGA-E2-A1LE	TCGA-A2-A1FW	TCGA-AR-A254	TCGA-A2-A04X	TCGA-PL-A8LV
TCGA-OL-A5D6	TCGA-AC-A23C	TCGA-BH-A18R	TCGA-AO-A03M	TCGA-AC-A2QH
TCGA-A2-A259	TCGA-EW-A1PD	TCGA-B6-A0IG	TCGA-AR-A0TQ	TCGA-A7-A26G
TCGA-LL-A7T0	TCGA-A8-A08F	TCGA-BH-A0W7	TCGA-C8-A1HF	TCGA-C8-A1HL
TCGA-A8-A09C	TCGA-AN-A0FJ	TCGA-BH-A0E2	TCGA-C8-A273	TCGA-A8-A08J
TCGA-B6-A1KF	TCGA-AO-A0JL	TCGA-A8-A092	TCGA-AO-A0JG	
TCGA-A2-A0CW	TCGA-A2-A4S3	TCGA-BH-A18V	TCGA-AO-A0J5	

ICGC: *BRCA1*- negative

Sample ID							
DO218489	DO227809	DO5801	DO1247	DO3799	DO217934	DO227943	DO224763
DO218488	DO2281	DO4515	DO2575	DO1136	DO1722	DO227944	DO5326
DO218478	DO2275	DO5843	DO44105	DO3388	DO217908	DO227945	DO5312
DO218457	DO227815	DO5836	DO227521	DO2055	DO1727	DO2389	DO224781
DO218428	DO227817	DO4509	DO44103	DO3382	DO1707	DO227947	DO224788
DO218419	DO227820	DO4503	DO44109	DO3376	DO1702	DO227948	DO5305
DO218404	DO2264	DO5829	DO44107	DO2043	DO1767	DO227949	DO224798
DO218408	DO2269	DO5822	DO1237	DO2049	DO1761	DO2383	DO5368
DO218502	DO3590	DO5815	DO1239	DO3370	DO1755	DO227950	DO4036
DO218583	DO227830	DO5884	DO2569	DO4695	DO1743	DO225306	DO4038
DO218560	DO227846	DO3221	DO44101	DO2032	DO1749	DO225305	DO4030
DO218553	DO227854	DO4551	DO2563	DO3364	DO217887	DO225304	DO5361
DO220824	DO227857	DO4557	DO1231	DO2037	DO1732	DO225303	DO4024
DO220826	DO227862	DO3215	DO3892	DO3352	DO1737	DO225302	DO5354
DO220825	DO225207	DO5877	DO1233	DO4683	DO217865	DO225301	DO4012
DO220820	DO225206	DO4545	DO3898	DO3358	DO1792	DO225300	DO4018
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