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REVIEW ARTICLE

ASSOCIATION OF BRCA2 POLYMORPHISM TO SCHIZOPHRENIA IN SAARC COUNTRIES: A SYSTEMATIC REVIEW

Kanwal Abbas Malik[1], Ishrat Aziz[1], Amna Abid[1], Saadat Ali[2]

[1]Department of Biology, Virtual University of Pakistan, Lahore, [2]Department of Molecular Genetics, Chughtai Laboratory, Lahore, Pakistan

ABSTRACT

Schizophrenia is a complex disorder of polygenic inheritance with a lifetime prevalence of 5-10%. An external study showed that the role of BRCA2 is needed for the normal neurogenesis in mice. Another recent meta-analysis showed that genetic polymorphism of BRCA2 could increase susceptibility to schizophrenia. This study conducted the possible relationship between BRCA2 polymorphisms in schizophrenic patients in participating SAARC (South Asian Association of Regional Corporation) countries (Pakistan, India, Sri Lanka, Nepal, Bhutan, Maldives, Bangladesh and Afghanistan). While conducting this review, we collected data from eight SAARC countries. We collected that articles which were published from 1997 to 2020, using PubMed, and NCBI databases to amplify data about the association of BRCA2 polymorphism to schizophrenia patients in SAARC countries. Totally 24 studies were included in this review. We have additionally reviewed fewer studies from other than SAARC countries to support the evidence concerning this issue. Major studies from each SAARC country have identified novel and pathogenic mutations in BRCA2 but have not assessed on BRCA2 polymorphism within schizophrenia patients. Yet, there is no conclusive evidence found regarding the association of BRCA2 polymorphism to schizophrenia.

KEY WORDS: BRCA2 Gene; Schizophrenia; Pakistan; India; Sri Lanka; Bhutan; Afghanistan; Maldives; Nepal; Bangladesh.

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INTRODUCTION

Schizophrenia is a severe mental illness which is considered a polygenic inheritance (multiple genetic inheritances) and some genes that show susceptibility at many genetic locations with small penetrance. The psychotic disorder has a lifetime prevalence of about 0.3%-0.7%.[1] Schizophrenia is distinguished by delusions, hallucinations and disordered speech and negative symptoms, including disinterest and flat affect.[2] Family and identical studies showed that the risk of illness is affected genetically and by environmental factors.[3,5] Schizophrenic patients are more likely to be physically inactive, have insufficient diet, and smoke heavily. These factors are related to the development of cancer, but studies regarding the association of schizophrenia and cancer showed contrary results.[3] Fewer studies have shown reduced incidence of cancer.[7,8] While other studies have found the increased rate of cancer in schizophrenia patients.[9,10] This severe mental disorder also has a poorly understood molecular genetic mechanism. Recently a study showed that polymorphism of DNA repair genes, including BRCA2, may be involved as significant contributors of pathogenesis in schizophrenia. The repairing mechanism of impaired DNA can increase the risk of schizophrenia and related cognitive dysfunction.[11]

In Pakistan prevalence of schizophrenia is still not known, due to conflict among the people. This disorder likely affects 1-2% of people.[12,13] In Pakistan, the major population lives in rural areas. Because of low literacy rate, the schizophrenic patient is thought as being possessed by an evil spirit. Very few studies have been conducted so far discussing this issue in Pakistan. Studies suggest the patient's consciousness about their illness may result in taking drugs and perceived social support.[14,15]

Corresponding Author:
Ishrat Aziz
Assistant Professor
Department of Biology
Virtual University of Pakistan
Lahore, Pakistan
E-mail: ishrat.aziz@vu.edu.pk

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BRCA2 gene is a DNA repair gene. Mutations occurring in the BRCA2 gene can cause a lifetime risk of breast cancer in female carriers, which may be same as that associated with BRCA1 mutations, having lower but statistically significant ovarian cancer risk. About 5-10% of breast cancers are hereditary and 30-50% are due to variations in BRCA1 (0MIM113705) and BRCA2 (OMIM600185) located respectively on chromosomes 17q21 and 13q21. The human reference BRCA2 gene contains 27 exons, and cDNA has 10254 base pairs that code for a protein of 3418 amino acids. Exon11 is the largest exon of BRCA2, which comprises over 50% of the entire BRCA2 gene. BRCA2 is considered to have a particular affinity for single and double stand DNA Junctions and in normal replication, are important for recombination repairs.[16]

Recently Genome Wide Association Study (GWAS)[17] found a significant association between schizophrenia and single nucleotide polymorphism in PALB2 that is partner and localizer of BRCA2 gene.[17] BRCA2 is located on chromosome 13 and encodes for the protein and this protein is involved in the repair of damaged DNA. Any mutation in the BRCA2 gene can lead to certain types of cancer.[18] Recently another study showed that normal neurogenesis in mice requires the role of BRCA2.[19] The finding suggests there is a casual relationship between PALB2 and BRCA2 with bipolar disorder and BRCA2.[11] Thus, it is possible that any alteration in BRCA2 may lead to severe psychiatric disorders, including schizophrenia, by causing abnormal neurogenesis. We have conducted this review to investigate the association of BRCA2 polymorphism to schizophrenia patients in SAARC countries.

MATERIAL AND METHODS

This study was conducted in Department of Biotechnology, Virtual University of Pakistan, Lahore from January 2021 to July 2021. This review represents a study population from eight SAARC countries. Articles from 1997-2020 were retrieved by using PubMed, Med line, NCBI databases for the English language published articles, to compile data regarding the current state of knowledge concerning the association of BRCA2 polymorphism to schizophrenia in SAARC countries. Following keywords were used such as BRCA2, schizophrenia, Pakistan, India, Bangladesh, Nepal, Bhutan, Sri Lanka, Maldives and Afghanistan. Total 25 studies were included in this review. We have additionally reviewed fewer other studies to support the evidence concerning this issue.

Selection criteria

We have searched all those studies addressing the association of BRCA2 polymorphisms in schizophrenia patients, BRCA2 polymorphism or variations or just schizophrenia in each participating country of SAARC. The reference list of selected studies was also reviewed to collect potentially important articles.

Data extraction

Two reviewers independently assessed articles for inclusion, extracted data and assessed quality. The general information extracted included first author, publication year, the ethnicity of the studied population, sources of controls and cases and BRCA2 mutations found in each study.

Mutational information of BRCA2 was collected from the NCBI database and larger cohort studies from participating SAARC countries. We also consolidated data from the World Health Organization, published literature concerning schizophrenia in SAARC countries (including Pakistan, India, Sri Lanka, Nepal, Bhutan, Bangladesh, Maldives, and Afghanistan). Pathogenic BRCA2 mutations, which affect the protein function, are also a part of this review.

BRCA2 mutational information was developed as following criteria.

- Date and year of the study
- Mutation type
- Type of study
- Number of cases
- Ethnicity of patients

The country where the novel mutations were found

Our review also included the unique mutations or polymorphism which is specific to the country. The distribution of BRCA2 mutations studied in each country was also recorded. Flow diagram of selected studies is shown in Figure 1.

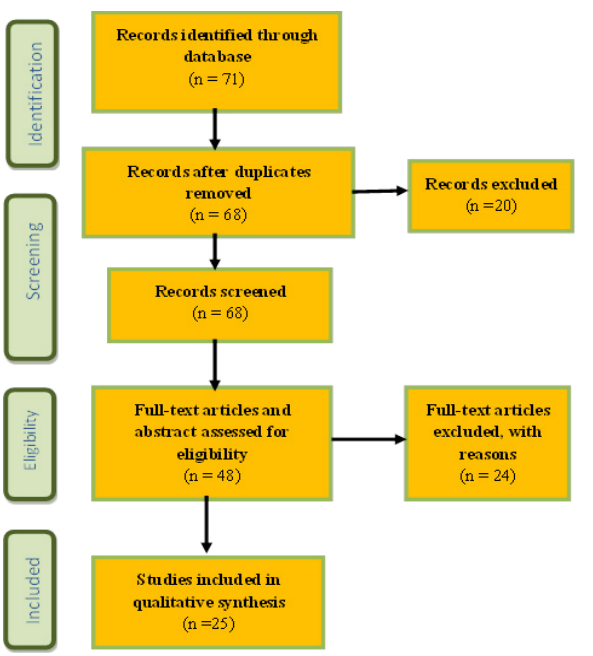

Figure1. Flow diagram for selected studies

METHODOLOGIES OF THE STUDIES INCLUDED IN THIS REVIEW

The methodology of Pakistani studies

Major Pakistani studies included in this study were assessed by Rashid, et al., 2006[20] and Liede, et al., 2002[21] described the mutation spectrum of BRCA2.

A study by Liede, et al., in 2002[21] at the National Centre Institute, Karachi and Jinnah Hospital, Lahore conducted a case-control study of 341women having breast cancer and as a control 200 women. From peripheral blood, the human genome was extracted. A protein truncation test was performed for an intron-exon boundary followed by direct Sequencing for confirmation of all mutant bands detected by PTT.

Another study by Rashid, et al., 2006[20] selected 176 patients with breast or ovarian cancer. The genomic DNA was extracted from blood samples. Coding regions of both BRCA1 and BRCA2 were screened by SSCP (single-strand conformational polymorphism analysis), DHPLC (denaturing high-pressure liquid chromatography), and PTT (protein truncation test). Sample showing variants by SSCP, DHPLC, or PTT, automated DNA sequencing was performed.

The methodology of Indian studies

Indian study by Vaidyanathan, et al., in 2009[22] carried out the mutational analysis in 61 subjects diagnosed with breast and ovarian cancer from South India with a family history. Mutational analysis was carried out using conformational sensitive gel electrophoresis (CSGE) followed by sequencing.

Another Indian study by Saxena, et al., in 2002[23] has collected 20 clinical based samples from Indian breast cancer patients, referred to the Department of Cancer Surgery, Safdarjung Hospital, New Delhi. Among these 20 patients, 13 had a family history of breast or ovarian cancer and six had the early-onset disease; one was a male breast cancer patient. All coding intronic and exon junction regions of the gene were screened for mutation by Heteroduplex analysis (HDA). Bands from the sample were amplified and sequenced using the USB-PCR product sequencing kit.

The methodology of Sri Lankan study

De Silva, et al., in 2008[24] studied sequence variations of BRCA2 in 149 participants. Direct sequencing of Exon 11 and sequencing of abnormal bands after screening with SSCP were used to find mutations.

The methodology of the study from Bangladesh

Parvin, et al., in 2017[25] has recruited 310 patients on hospital bases having breast cancer and as a control 250 women of matching age were also enrolled. To analyse genetic polymorphism; polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) was used.

There was no study found in other SAARC countries such as Nepal, Bhutan, Maldives and Afghanistan, which had assessed the examination of BRCA2.

RESULTS

To date, there was no study found in SAARC countries which have assessed the association of BRCA2 polymorphism in schizophrenia patients. However, fewer evident studies were included in this review to provide evidence of the issue. Characteristics of these studies are listed in Table 1.

Mutations of BRCA2, specific to the region have been assessed in the major pioneering studies in different SAARC countries and described in this review (Table 2). Still no study was found in some SAAR countries; Nepal, Bhutan, Maldives, and Afghanistan.

Liede, et al., in 2002[21] identified 11 BRCA2 mutations in his study. Among these 341 patients, eight mutations were found in BRCA2, and among the 120 women, three mutations were found in BRCA2. Observations showed that ten mutations out of 11 were distinct, and eight mutations from these ten distinct mutations were unique to the Pakistani population and are stated in Table 2. Rashid, et al., in 2006[20] studied 176 patients selected based on family history found 7 BRCA2 mutations from which 5 were novel mutations and were not found in healthy countries.

An Indian study by Vaidyanathan, et al., in 2009[22] found only two BRCA2 mutations but no association between BRCA1 and BRCA2 mutations with cancer

Table 1: Characteristics of the evidence studies on the association of BRCA2 polymorphism to schizophrenia in SAARC countries

References	Country	Type of study	Study title	Results
Frappart, et al., 2007[19]	United Kingdom	Experimental	BRCA 2 is required for neurogenesis and suppression of medulloblastoma.	BRCA2 is important for the nervous system development and highlights the tissue specific requirements for DNA repair factor.
Tesli, et al., 2010[11]	Norway	Case Control	Association analysis of PALB2 and BRCA2 in Bipolar disorder and Schizophrenia in a Scandinavian case-control sample.	Alteration in PALB2 and BRCA2 leads to developing BD and SCZ.

BD, bipolar disorder; SCZ, schizophrenia

type was found. One modification was novel in identified BRCA2 mutations while the other was reported mutation. Another Indian study by Saxena, et al., in 2002[23] stated that two BRCA2 missense variants were found in more than one patient and likely represented population specific polymorphism. (Table 2)

A study of Bangladesh by Parvin, et al., in 2017[25] found that BRCA2 and other candidate genes (BRCA1, RAD51rs1801320, and HER2rs1136201) were associated with breast cancer in the study population.

Sri Lankan study by De Silva, et al., in 2008[24] included in this review found 23 sequence variants of BRCA2 participants. Two variations were identified as novel pathogenic frameshift variations, which were commonly occurring in the BRCA2 among Sri Lankan familial breast cancer patients. These pathogenic mutations are listed in Table 2.

DISCUSSION

In conducting this review, published data was collected through a literature search. This is the most recent review of association between BRCA2 polymorphism and schizophrenia in SAARC countries accessible to our knowledge.

Other studies from other than SAARC population; Tesli, et al., in 2010[11] and Frappart, et al., in 2007[19] have investigated the association between BRCA2 polymorphism in schizophrenia patients.

Tesli, et al., in 2010[11] have conducted a meta-analysis where he investigated the association of PALB2 and BRCA2 polymorphism in bipolar disorder and schizophrenia in a Scandinavian case-control sample. They analysed the PALB2 SNPrs420259 and BRCA2 SNPrs9567552 in bipolar disorder and schizophrenia patients. However, they found a strong association between these two SNPs with bipolar disorder but did not found any relationship within schizophrenia patients.

Another study found that BRCA2 was required for the normal neurogenesis in the mouse brain; particularly in the cerebellum. This study investigated the role of BRCA2 in brain development in the mouse. While considering the importance of BRCA2 in homologous recombination and associated with germline inactivation, they found that inactivation of BRCA2 results in microcephaly associated with defects in neurogenesis. Particularly during development, they were highlighting the tissue specific requirement for DNA repair during neurogenesis.[19]

Table 2: Studies regarding association of BRCA2 polymorphism to schizophrenia in SAARC countries

References	Country	Number of Cases	Type of study	Method	Identified BRCA2 mutation	Association with SCZ
Rashid, et al., 2006[20]	Pakistan	176	HB	SSCP, DHPLC	1993delAA L992X 4052delTAGA E1912X	None
Liede, et al., 2002[21]	Pakistan	341 120	Case Control	PTT	3337C->T 5950delCT 669delTC	None
Saxena, et al., 2002[23]	India	20	CB	PCR	8345A>G 5007A>C	None
Vaidyanathan, et al., 2009[22]	India	61	FB	CSGE, PCR	4866insT 6079delAGTT	None
Parvin, et al., 2017[25]	Bangladesh	310	HB	PCR RFLP	-	None
De Silva, et al., 2008[24]	Sri Lanka	149	FB	PCR direct sequencing	IVS8 – 1G 2403insA 2667insT	None

Br, breast cancer; Ov, ovarian cancer; SSCP, single strand conformational polymorphism; DHPLC, denaturing high pressure liquid chromatography; PTT, protein truncation test; RFLP, restriction fragment length polymorphism; PCR, polymerase chain reaction; CSGE, conformational-sensitive gel electrophoresis; HB, hospital-based; FB, family-based; CB, clinical based; SCZ, schizophrenia

Data interpretation concerning the association of BRCA2 polymorphism in schizophrenic patients is complex. There was no evident study in the SAARC countries that we could present in this review. Much work has been done on schizophrenia, and BRCA2 polymorphism in SAARC countries, major work done on BRCA2 polymorphism in SAARC countries is discussed in Table 2. Still, the association between these two was not assessed even in the single study. However, two outer studies were included in this review to support the issue.[11,19] Characteristics of these studies are listed in Table 1.

No study was found which have assessed BRCA2 polymorphism in some SAARC countries, including Nepal, Bhutan, Maldives and Afghanistan.

CONCLUSION

This review has quick access to the most recent scenario on the association between BRCA2 polymorphism to schizophrenia. To the present date, no study was found where the association between BRCA2 polymorphism and schizophrenia in the eight participating SAARC countries has been examined. Two outer studies were included to support the evidence. Many work and studies on a large scale are required to address this issue and validate this review results.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	KAM, IA
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.