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Association of FGFR2 rs2981582 Polymorphism with Breast Cancer Risk among Sudanese Patients: Implications for Predictive Biomarker Development

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Abstract

Background: The rs2981582 C/T is an intronic single nucleotide polymorphism in the Fibroblast Growth Factor Receptor 2 gene has been constantly associated with an increased risk of susceptibility to breast cancer.
Aim: The current study targeted the frequently reported C/T SNP (rs2981582) of *FGFR2* gene to test the role of this SNP in the susceptibility to breast cancer in Sudanese women. We evaluated the role of *FGFR2* gene polymorphism (rs2981582) and some non-genetic risk factors on the risk of breast cancer among Sudanese females. We also evaluated the interactions between known risk factors and C/T SNP of *FGFR2*.
Methods: This is a hospital based case control study. DNA was extracted and PCR-RFLP data from 81 cases and 81controls were analyzed.
Results: The risk allele (T allele) of the rs2981582 polymorphism was associated with an increased risk of breast cancer (*P-value*= 0.0024) (OR =2.2, CI95%=1.34 to 3.53). Significant association was also encountered between cases carrying this polymorphism and history of benign tumors (*P-value* = 0.0001), also significant association was found between cases carrying this polymorphism and have family history of breast cancer in first degree relatives (*P-value*=0.045*)* (OR==7.22 CI95%=1.047 to 81.2).
For genotype risk assessment, breast cancer risk significantly increased with TT genotype *(P-value* =0.0018) (OR=1.711 CI95%=1.16 to 4.04) when compared to the other two genotypes (CC and CT).
Conclusions: Although our findings of this study are promising and suggesting that *FGFR2* rs2981582 is significantly associated with breast cancer susceptibility in Sudanese women, but this study alone is not sufficient and further cohort studies are needed to confirm these findings and the possibility of using the rs2981582 in the future as a potential biomarker for breast cancer prediction as diagnostic tool.
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Key words: Breast Cancer, FGFR2, Sudanese and SNP.

Introduction

Worldwide, breast cancer is the most commonly diagnosed cancer in women, and it is the second type of cancer that leading of deaths (Jemal *et al*., 2011: Arnold *et al.*,2002). Sudan is like other African and sub-Saharan countries is experiencing a growing breast cancer epidemic and the problem is complicated by challenges that are distinctive of developing countries (Elamin *et al*., 2015: Sharma, 2021). The incidence of breast cancer has dramatically increased in Sudan and the number of new cases is increasing each year (Elebead *et al*., 2012: Ahmed *et al.*, 2024) and it was very close to that found in countries with known high incidence of breast cancer such as Sweden, UK and USA (Globocan (2020): American Cancer Society (2022)).

It is most redundant among younger females and has poor prognosis representing an African background phenomenon or simply late management. In fact, 78 % of Sudanese cancer patients are officially diagnosed at stage III or IV of the disease (Ahmed *et al*., 2010: Hayat *et al.*, 2021).

Attempts to understand the etiology of breast cancer are expanding to include new potential markers of disease

risk. Efforts are hampered by diversity in the frequency of breast cancer among different ethnic groups, a fact that was reported early in Sudan (Awadkareem *et al*., 2012: Idris *et al*., 2025).

High penetrance genes (*BRCA1/2*) account for up to 10 % of cancer risk (Easton *et al*., 2007), yet few mutations have been identified in those genes among Sudanese (Masri *et al*., 2002, Awadkareem *et al*., 2012). Likewise, the data on *BRCA* gene mutations in Africans in general is sparse and the mutational spectrum of *BRCA1/ 2* in African is not well characterized as that of Caucasians (Ferla *et al*., 2007: Oluwagbemiga *et al*., 2012). On the other hand, the outstanding predisposition to breast cancer and the poor prognosis among Africans is likely to be polygenic and may include multiple other common low-penetrance alleles, rare intermediate-penetrance genes, and rare low penetrance alleles (Turnbull and Rahman, 2008: Sharma, 2021).

Advances made lately using GWAS studies paved the way for an accelerated discovery of other low penetrance genes. Nearly 70 loci show significant association with breast cancer risk in genome-wide association studies (GWAS) (Michailidou *et al*., 2013: Mortezaei and Tavallaei, 2021). Several of studies have identified fibroblast growth factor receptor 2 (*FGFR2*), a gene involved in mammary gland development, as a novel gene for breast cancer risk. The gene interestingly showed consistent positive association with breast cancer risk regardless of ethnic variation indicating a common mechanism of this gene with low variability across different genetic backgrounds (Haugsten *et al*., 2013).

FGFR2 is localized on chromosome 10 and it encodes for a protein involved in vital processes such as embryonic development, cell division, regulation of cell growth, maturation, formation of blood vessels, and wound healing (Koziczak *et al*., 2004: Nicotera *et al*., 2023).

Alterations in the expression of the *FGFR2* gene are associated with certain cancers through enhancing cell division, cell movement, and the development of new blood vessels that nourish a growing tumor (Basilico and Moscatelli, 1992).

A locus within an intron of the *FGFR2* (fibroblast growth factor receptor 2) gene is consistently strongly associated with breast cancer risk (Hunter *et al*., 2007: Chawisangzeli *et al*., 2021). One of the strongest and most consistent genetic risk factors for breast cancer is an intronic single nucleotide polymorphism (SNP) in the *FGFR2* gene, rs2981582 (Koziczak *et al*., 2004: Balmukhanov, 2015). The risk appears to be consistent in Caucasian, (King *et al*., 2004; Meyer *et al*., 2008; Gold *et al*., 2008) and Asian (Rhodes *et al*., 2004). Accordingly, rs2981582 was observed to be associated with *FGFR2* expression in breast cancer tissues (Meyer *et al*., 2008: Balmukhanov, 2015: Sun *et al*., 2010).

Several but insufficient studies addressed breast cancer different characteristics among Sudanese, yet, real risk factors and genetic components of the disease are far from being considered. The current study targeted the frequently reported an intronic C/T SNP (rs2981582) of FGFR-2 gene to test the role of this SNP in the susceptibility to breast cancer in Sudanese women. We also evaluated the interactions of some known risk factors and C/T SNP of *FGFR2*.

Methods

This is a hospital-based case control study comprising of 162 genetically unrelated Sudanese women including 81 randomly selected breast cancer cases obtained from Radiation and Isotopes Center Khartoum (RICK) and 81 healthy matched controls (same population, age, sex and ethnic groups) from community.

Ethical approval had been obtained from the Ministry of Health and after informed consent participants were interviewed and asked to completed questionnaires about their lifestyles and reproductive history.

3 ml of venous blood samples were collected in EDTA tubes and DNA was extracted following Phenol Chlorophorm method (Sambrook and Russell, 2001). Briefly, two ml of blood were taken and mixed with 10ml of Red Cell Lysis Buffer (RCLB) (1mM NaHCOR3 and115mM NHR4RCl) and centrifuged at maximum speed for 5 minutes. The supernatant was discarded and the pellet was washed for a second time with 10 ml RCLB.

The white pellet was lysed with 2 ml of White Cell Lysis Buffer (100mMTrisHCl, 5mM EDTA, 50mM NaCl and 0.2% SDS), mixed with 2µl of Proteinase k (20 mg/ml) and then incubated overnight at 37°C. After that, equal volume of Phenol Choloroform Isomyl Alcohol (25:24:1) was added, mixed and centrifuged at maximum speed for 6 minutes. Equal volume of Choloroform Isomyl Alcohol (24:1) was added to the supernatant and centrifuged at maximum speed for 6 minutes. The supernatant was transferred into a new tube and 1:10 of Sodium Acetate was added. Sample was mixed with double volume of 95% Ethanol to precipitate DNA and then samples were kept overnight at -20°C. The refrigerated solution was centrifuged at maximum speed for 5 minutes, and then the supernatant was poured off. Pellet was washed with 2 ml of 70% Ethanol, air dried and re-suspended in 100 µl of Double Distilled Water. DNA samples were quantified using Nanodrop Spectrophotometer (ND.1000 v3.5.2) at 260nm and finally were stored at -20°C.

Genotyping of rs2981582

A set of primers was designed to amplify the *FGFR-2* gene using the Polymerase Chain Reaction. The sequences of these primers permitted the amplification of a 262 bp DNA fragment of the *FGFR-2* gene including the SNP of interest (rs2981582 C/T). The PCR primer sequences used were as follows: *FGFR2* F 5' CGTGAGCCAAGCCTCTACTT-3' and

FGFR-2 R 5' TAAGTGTGCTGTTCATTCA-3'

PCR reactions were performed using 1µL of DNA samples, 2 µl of each primer (I0 µM), 12.5 µl of 2X Taq Master Mix (Vivantis) and 9.5 µl of ddH_2O in a total volume of 25 µl. The 2X master mix consisted of Taq DNA polymerase (0.05U/µl), 2X Vibuffer A, o.4mM dNTPs and 3.0 mM MgCl2.

The PCR amplification was performed in a programmable thermocycler (G-STORM 482). PCR was performed using the following program profile: 94 °C for 2 min, 35 cycles of: 10 s at 94 °C, 30 s of annealing (Annealing temperature was 65°C), and 1 min of extension at 72 °C. Finally, the reaction was ended with 5 min at 72 °C.

Five µl of the PCR product were loaded into a 2% agarose gel. A band of 262 bp was visualized by Ethidium Bromide staining under UV using a gel documentation system. PCR products were subjected to restriction digestion by (Aci1) (10U/µl) restriction enzyme (Thermoscientific) to differentiate between the three different genotypes (CC, CT, and TT).

Electrophoresis of the restriction products was performed on a 3% agarose gel and stained with Ethidium Bromide.

Statistical analysis

Statistical Packages for Social Science (SPSS) software were used for all statistical analysis. Hardy–Weinberg equilibrium (HWE) was conducted to test the sampling technique and evaluated by a goodness-of-fit X^2 test. For Associations between individual genotypes and breast cancer risk Chi-square test was used, and for relative risk analysis (RR), odds ratios (ORs) and 95% confidence intervals (CIs) Fisher's exact test was performed (Graph pad prism version 6.07).

Results

The current study included 81 healthy population control and 81 sporadic breast cancer cases with mean age of 40.6951±0.9940 years among cases and 41.0988±1.21926 years in controls.

The majority of cases and controls were married comprising 93.90% of cases and 86.42% of controls. The mean of menstruation age was 14.00 ± 0.1533 years in cases and 14.74 ± 0.1962 years in controls with significant difference (*P-value*=0.0059). Significant differences were also reported when menopausal status was compared in both groups. In which 71.95% of cases were post-menopausal in comparison to 18.51% of controls (*P-value*=0.000). The mean of postmenopausal age was 42.55 ± 0.8585 years in cases and 49.27 ± 1.136 years in controls (*P-value*=0.0004).

Cases reported significantly higher abortion rates in fetus of more than 5 months (17.07%) compared to 3.70% in controls (*P-value*=0.008).

Regarding personal history of benign breast tumors, cases had significant higher percentage of benign tumors when compared with controls (P-value=0.0001) (RR=2.99 at CI 95%=1.83 to 2.88) as shown in table1. Likewise, cases

who had breast cancer in first degree relatives had about four times risk of developing the disease (*P-value*=0.0223*)* (OR=3.963, CI 95%=0.244 to 12.62). As expected significant differences were found when we combined individuals who had family history of cancer and benign tumors (*P-value*=0.0001). Almost 50% of participants of the current study were of western Sudan ancestry with no significant differences between cases and controls (P-value=0.782). Table 1 summarizes the demographic data of both cases and controls.

Table 1: Demographic data of both cases and controls

Characters	Cases	Controls	*P*-values
Mean age of married	21.50±0.7559	21.67±0.546	0.8517
Mean of menstruation age	14.00 ± 0.1533	14.74 ± 0.1962	**0.0059**
Mean of menopausal age	42.55 ± 0.8585	49.27 ± 1.136	**0.0004**
Abortion	17.07%	3.7%	**0.008**
Personal history of benign tumors	34.14%	2.46%	**0.0001**
Family History of breast cancer	17.07%	4.93%	0.0223

Genotype analysis

The observed genotype frequencies were found to be at Hardy–Weinberg equilibrium ($\chi 2$ test, P>0.05) in both groups.

PCR reaction produced a band of the expected 262 bp size (Fig. 1) . The three possible genotypes expected when this biallelic locus is digested with Aci1 restriction enzyme (homozygous CC ancient genotype, the heterozygous CT, and homozygous variant TT) are shown in Fig. 2.

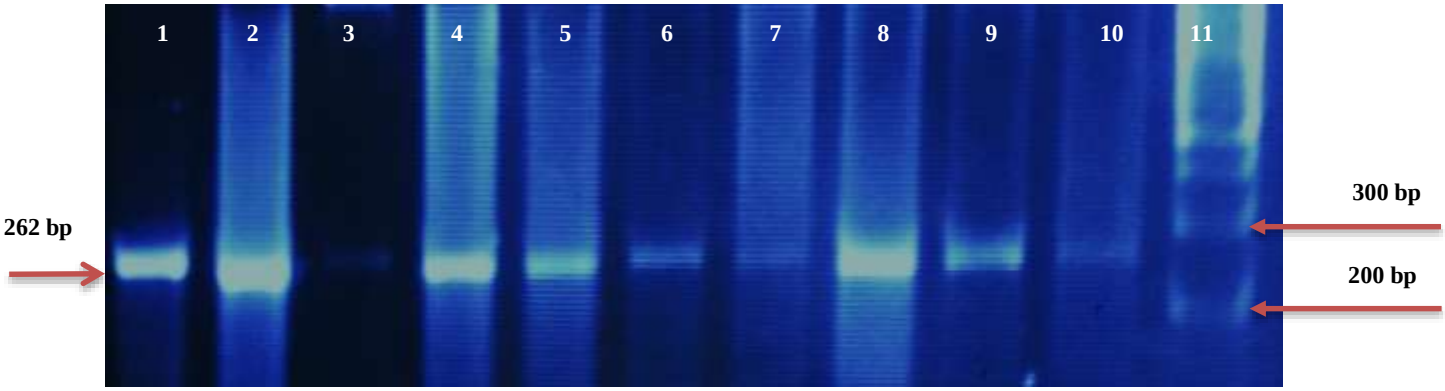

Figure 1: Gel electrophoresis of PCR products of *FGFR2 gene* intron *2* (band at 262 bp). Lane 11; DNA Ladder 100 pb. Lanes 1-10; PCR products

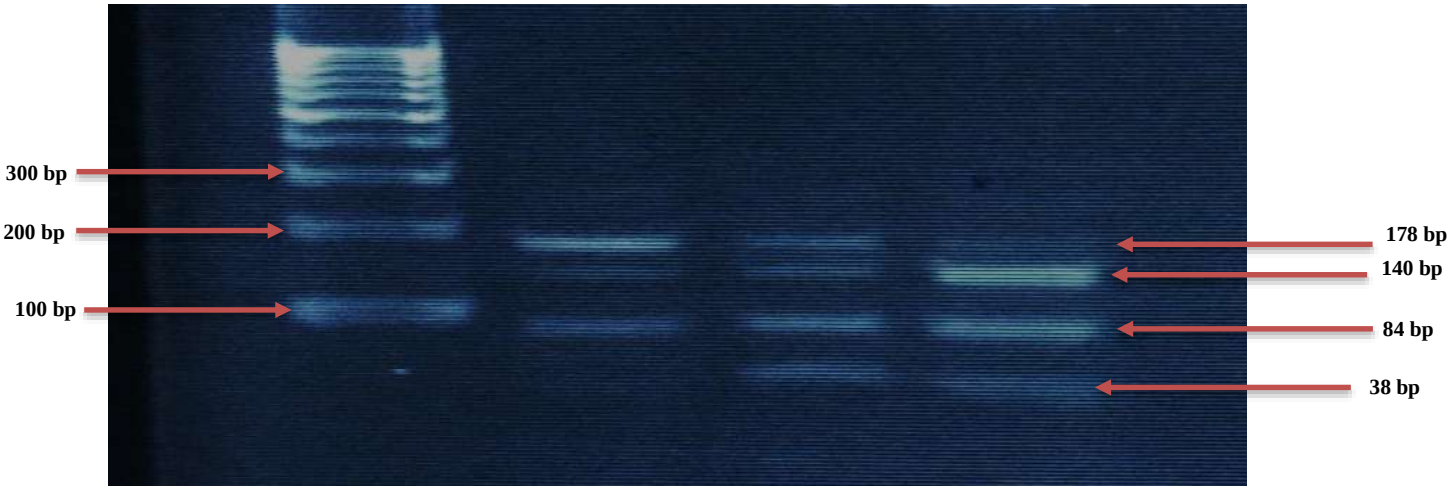

Figure 2: Gel electrophoresis of PCR product in 2% agarose after digestion with Aci1 restriction enzyme. Lane 1; 100bp DNA ladder, Lane2; homozygous mutant TT (178bp and 84bp), Lane3; heterozygous CT (178,140,84and 38bp) and lane4; homozygous ancient (140,84and 38).

Genotype frequencies of the different allele combinations in cases were 1.23%, 41.9% and 56.79% and 9.7%, 56.79% and 33.33% for the controls for the CC, CT and TT genotypes respectively (Table2). Chi-square test depicted a significant association for the *FGFR2* rs2981582 SNP with breast cancer risk (*P-value* =0.0018) (OR=1.711 CI95%=1.16 to 4.04) (Table 1). The frequency of the ancestor allele was 22.22% and 38.27% for cases and controls respectively, while, the risk allele reported 77.77% in cases versus 61.73% in controls. The T Allele was found to increase the risk of developing breast cancer (*P-value*=0.0024) (OR=2.2, CI=1.34to 3.53) (Table 2).

Table2: Percentages of allele's frequencies of *FGFR-2 rs2981582* in study population. Significant differences were observed d and the risk allele (T allele) show higher frequency in cases.

Code	Allele frequency (%)		Genotype frequency (%)		
	C(%)	T(%)	CC (%)	CT (%)	TT (%)
Cases N=81	36 (22.22%)	126 (77.78%)	1 (1.23%)	34 (41.97%)	46 (56.79%)
Controls **N=81**	62 (38.27%)	100 (61.73%)	8 (9.87%)	46 (56.79%)	27 (33.33%)
P-Value	C%=97(30.24%) T%=180(69.75%) **P.value=0.0017**		C%=97(30.24%) T%=180(69.75%) **P.value=0.0023**		

Significant differences were observed when we analyzed some of demographic data with three possible genotypes, the risk allele (T allele) was significantly associated with northern ancestry of cases when compared to controls (P-value=0.0043). Risk allele (T allele) was also associated

significantly with cases who had history of benign tumors
(*P-value*=0.000) (Table3).

Table 3: Demographic data and genotype frequencies of both cases and controls

Variables	CC%		CT%		TT%	
	Cases	Controls	Cases	Controls	Cases	Controls
Origin						
North	1.23%	6.09%	6.09%	19.75%	22.22%	11.11%
East	0%	0%	0%	2.46%	3.70%	1.23%
West	0%	3.70%	29.62%	25.92%	28.39%	19.75%
Center	0%	0%	4.93%	8.64%	3.70%	1.23%
P- values	0.99		0.078		0.82	
Pregnancy						
Yes	0%	7.40%	35.80%	46.91%	46.91%	27.61%
No	1.23%	0%	4.93%	7.40%	7.40%	2.46%
P- values	0.142		0.99		0.702	
Abortion						
< 5 months	0%	1.23%	17.28%	19.75%	1.23%	11.11%
≥5 months	0%	0%	11.11%	2.46%	0%	1.23%
P- values	0.99		0.075		0.99	
Menstruation						
<14 years	1.23%	4.93%	28.39%	20.98%	44.44%	17.28%
≥ 14 years	0%	4.93%	13.58%	35.80%	13.58%	16.04%
P- values	0.99		**0.0123***		**0.0397****	
History of benign tumors						
Yes	0%	1.23%	18.51%	1.23%	17.28%	0%
No	1.23%	8.64%	23.45%	55.55%	39.50%	33.33%
P- values	0.99		**0.0001*****		**0.001******	
Family history of breast cancer	1.23%	2.46%	4.93%	1.23%	12.34%	1.23%
Yes	0%	7.40%	37.03%	55.55%	44.44%	32.09%
No						
P- values	0.33		0.15		**0.045*******	

* OR=3.567 CI95%=1.35 to 8.71, RR=2.09 CI95%=1.21 to 3.75
** OR=3.03 CI95%=1.06 to 8.05, RR=1.50 CI95%=1.04 to 2.643
*** OR=35.53 CI95%=5.66 to 382, RR=3.158 CI95%=2.10 to 4.76
**** RR=1.84 CI95%=1.39 to 2.13
***** OR=7.22 CI95%=1.047 to 81.2, RR=1.56 CI95%=1.035 to2.049

Discussion

Breast cancer is a result of a number of risk factors that are required for the disease to instigate and proceed. Genetic background dictates the outcome to produce a characteristic phenotype that might help in prevention, management and understanding of disease mechanisms. Yet, none of the known risk factors have shown to cause the rapid increase of the incidence of the disease among younger aged females or the poor prognosis observed among Sudanese as opposed to other populations.

In the current case–control study, the rs2981582 SNP was targeted to identify possible role in sporadic breast cancer among Sudanese patients. The risk allele (T) was found to be significantly associated with increased breast cancer risk. Females carrying at least one copy of the risk allele had two times risk of developing breast cancer. The reported risk in this study is among the highest scores compared to values published in recent meta-analysis concerning the entire intron (Zhang *et al*., 2017: Santhosh *et al*., 2023).

Despite the fact that most of study population were of western origin, patients of Northern origin pop out with a significant association with the T risk allele (RR=2.8, 95% CI=1.366.49) which is in promise with other reports that suggest a high incidence rate of breast and other cancers among Northern ethnic groups in comparison to other states of the Sudan according to cancer registry data at RICK (Ibrahim, 2002). Many reports indicated no significance differences in factors like demographical, hormonal, and family history related risk factors between women living in the Northern States compared to women from other states treated at RICK (Mohammed, 2013).

Regarding the relation between menstrual cycle and breast cancer risk, cases had significantly younger ages at menstruation and at menopause. In agreement with others (Collaborative Group on Hormonal Factors in Breast Cancer, 2012: Martinez *et al.,* 2019) whose findings confirmed that young age at menarche and old age at menopause increase breast cancer risk. Knowing that thirty percent of cases experienced termination of menstruation period after chemotherapy clarifies the detected significant association between menopausal status and breast cancer in this study (Martinez *et al.,* 2019).

The current study reports that personal history of benign tumors significantly increased the risk of breast cancer by twenty times. Prior studies of benign breast disease have focused on the risks for subsequent breast cancer associated with benign lesions and they also found significant association between benign tumors and breast cancer risk (Cheng *et al*., 2009). The risk allele was also significantly associated with cases who had history of benign tumors and who were married when compared to controls (Easton *et al.,* 2007: Hunter *et al.,* 2007). Significant increased risk was observed when we combined individuals who have family history of breast cancer in first degree relatives and history of benign tumors among cases and controls (*P-value*=0.0001).

Individuals with a first degree relative family history of breast cancer were seven times more susceptible to the disease. Another study was in confirmed with our results reporting significant association of *FGFR2* and breast cancer among those with a history of breast cancer in a first degree family member (Turner and Grose, 2010).

The fact that *FGFR2* SNP affects breast cancer risk in Sudanese patients, presents enough encouraging evidence suggesting that targeting *FGFR2* in breast cancer could be a valuable approach in the future.

The intronic location of rs2981582C/T SNP suggested that it affects the risk of breast cancer through differential expression. Aberrant expression of alternatively spliced isoforms of *FGFR2* has been shown to activate signal transduction leading to transformation in breast cancer cells (Siddiqui *et al.,* 2014: Chawisangzeli *et al*., 2021). It has been proposed that conserved putative transcription-factor binding sites, lies in close proximity to the rs2981582 SNP, can potentially drive endogenous gene expression (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Testing that possibility using PROMO software indicated that no transcription factors are affected by the rs2981582 SNP thus the precise mechanism of how this SNP affect *FGFR2* up

regulation remains unclear (Turner and Grose, 2010). One possibility is the presence of other causative SNPs at proximity to the rs2981582 SNP. Analysis of African American population indicated that the close rs2981578 SNP (in LD with rs2981582 SNP), previously been implicated in up regulating *FGFR2* expression, is strongly associated with breast cancer (Liang *et al.*, 2015).

Although receptor status was not available for all cases in the current study, reports of receptor phenotypes in Sudanese patients seams to represent a spectrum of variation. While Ahmed et al. (2007) reported 90% and 77.5% positive ER and PR rates respectively (Ahmed e*t al*., 2007) reported dominance of negative ER/PR phenotype among Sudanese patients (Elgaili *et al*., 2017). This wide range might indicate phenotypic heterogeneity or technical inaccuracies (Ahmed e*t al*., 2007: Lei and Deng, 2017).

Conclusions

This was a pilot study to evaluate the associations of breast cancer susceptibility loci in Sudanese women. Our findings suggested that *FGFR2* rs2981582 was associated with breast cancer susceptibility. Although, findings of the present study are promising and suggesting that *FGFR2* rs2981582 is significantly associated with breast cancer susceptibility in Sudanese women but this study but it is unlikely to have any immediate clinical implications, however, further cohort studies are needed to confirm these findings and the possibility of using the rs2981582 in the future as a potential biomarker for breast cancer prediction as diagnostic tool. Such studies may play a key role in elucidating the biological mechanism that underline breast tumor formation, which may ultimately lead to improved treatment and prevention.

The significant association of *FGFR2* intron 2 SNPs with breast cancer risk, as well as their interaction with various clinical parameters revealed their contribution to breast cancer susceptibility among Sudanese population. To our knowledge this is the first study in association between rs2981582 polymorphism in the *FGFR2* gene and the risk of breast cancer in Sudanese women, however further research in order to better understand the association between *FGFR2* SNPs and its possible interaction with the risk of breast cancer. Further epidemiological and experimental studies of larger data sets along with sub-categorization by clinical parameters and expression studies are warranted to explore and confirm the role of these variants in increasing breast cancer risk that will help us better understand the genetic heterogeneity of complex diseases like breast cancer.

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