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Original Article:

Association of Quantitative and Qualitative Dermatoglyphic Variable and DNA Polymorphism in Female Breast Cancer Population

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Abstract: Objective: To investigate the association between dermatoglyphics and the DNA repair genetic variants in female breast carcinoma. Methodology: The distinct dermatoglyphic variables include ≥ six whorls, Finger ridge counts, A-B Ridge Count, ATD angle and Pattern intensity Index are analyzed for its association with the DNA repair variants namely XRCC1 Arg194Trp, XRCC3Thr241Met, ERCC4Arg 415Gln, and ERCC5 Asp1104His. The statistical procedure used to analyze the frequency of association is odds ratio and relative risk ratio. Result: The results suggests that the relative risk is about 2 to 4 times with statistical significance for breast cancer and high risk group for the genes XRCC1 Arg194Trp, ERCC4 Arg 415 Gln, ERCC5 Asp1104His in their dominant model in both breast cancer and high risk group for six or more whorls, Pattern Intensity Index, A-B RC. Conclusion: It can be suggested that dermal ridges can be used as an effective biomarker of genomic instability in breast cancer.

Key Words: Dermatoglyphics, DNA repair gene, single nucleotide polymorphism, breast cancer, genetic instability

Introduction:

Breast Cancer is a complex multi-factorial disease. The distribution of the status varies between populations based on their life style, environment, socio-economic status, awareness and quality of medical care. The Breast cancer incidence peaks in Asia among women in their 4th decade of life. In United States and Europe, it peaks among women in their 6th decade. Cancer statistics in Indian women is 25-30 and the age adjusted rate is 30-35 new cases per 100,000 women per year.(1-3) The causative factor of breast cancer cannot be definitely defined still. It involves the combination of both genetic and environmental factor. More number of genes are reported to be responsible for breast cancer. It becomes a very complex, costly and time consuming process to perform genetic testing and it involves follow up too. On the other hand research on dermal ridge patterns are becoming evident as it has got specific association with breast cancer. Dermal ridge patterns are said to act as a biomarker of our gene. It reflects the DNA pattern and the genetic instability. The different variables of dermal ridges in different areas of palm reflect the condition of specific gene.(4-7)

Methodology:

The study is being conducted among 150 females in three groups, each comprising of 50, carried out in the Department of Anatomy, ACS Medical College and Hospitals, Dr.MGR Educational and Research Institute, University, Department of Industrial Biotechnology, Dr. MGR Engineering and Research Institute, Dr.MGR Educational and Research Institute University, Tamilnadu, India, and Saveetha Medical College and Hospital, Saveetha University, Chennai, Tamilnadu, India. The participants are age matched between 35-60 years. The study commenced after getting approval from the Institutional Human Ethical Committee, Saveetha University - IHEC No-06/10/2012, Dated -09th October 2012. Chennai, Tamilnadu. The participants are given detailed explanation about the procedure and their co-operation and willingness is obtained with an informed consent.

The participants are grouped based on selection criteria. Group I includes females diagnosed histopathologically for breast cancer as their primary site of carcinoma. Group II includes females who are a categorized as high risk for breast cancer based on their family history for breast cancer (mother, sister or daughter) or any two criteria based on their endogenous exposure to estrogen which includes Menstrual history (early menarche below 12 years, late menopause above 50 years) Parity status (First Full Term Pregnancy – FFTP above 30 years of age, Nulliparity), Personal history of fibro-adenoma, obesity, Hormone Replacement Therapy (HRT). Group III includes normal healthy females. The exclusion criteria for group I &II includes breast cancer developed as secondaries from primary site of origin elsewhere, population exposed to chemotherapy or radiation therapy, population affected with any other major health problem, Male participants and those who do not possess proper visible dermal ridges due to their occupation. The exclusion criteria for group III includes personal or family history of breast cancer, Personal or family

history of non-malignant tumor, population exposed to chemotherapy or radiation therapy, population affected with any other major health problem, Male participants, and those who do not possess proper visible dermal ridges due to their occupation.

The data for dermatoglyphic analysis are collected using digital photography and the different variables are analyzed using computer. After the detailed analysis of various dermal ridge patterns, the distinctive dermatoglyphic variables are used as an outcome measure to assess its association with single nucleotide polymorphism (SNP) status of four DNA repair genes. The DNA repair variants namely XRCC1 Arg194Trp, XRCC3Thr241Met, ERCC4Arg 415Gln, ERCC5 Asp1104His are analyzed for the study population. The data collection procedure includes collection of 3ml of peripheral blood in EDTA coated test tubes through venipucture. The procedure includes extraction of DNA, followed by amplification of specific gene segments using Polymerase Chain Reaction and identification of polymorphism using Restriction Fragment Length Polymorphism. The frequency of appearance of all genotypes namely homozygous wild, heterozygous mutant and homozygous mutant genotypes are assessed and the frequency of breast cancer and high risk population are compared with control group. The distinct dermal ridge variables include ≥ six whorls, Mean Finger Ridge Count (MFRC), Total Finger Ridge Count (TFRC), A-B Ridge Count, ATD angle, Pattern Intensity Index-Digital (PII-D). All the dermal ridge parameter is assessed individually for its association with all the four SNPs. The frequencies of appearance of all the genotype for each distinctive dermal ridge variables are analyzed.

Data Analysis:

The statistical procedure used to analyze the frequency of association between Dermatoglyphic Pattern and Variant Allele of DNA Repair Gene is odds ratio, relative risk and the level of significance using P- value.

Results:

The distinct dermatoglyphic parameters are six and more than Six Whorls, Mean Finger Ridge Count (MFRC <12.6), Total Finger Ridge Count (TFRC<126), A-B Ridge count (<34.8), ATD Angle (<43°), Digital Pattern Intensity Index (PII-D>12.5). Dermatoglyphic variables Six and more than six Whorls, Mean Finger Ridge Count (MFRC<12.6), A-B Ridge count (<34.8) and Digital Pattern Intensity Index (PII-D >12.5) are associated with significant difference p<0.05 with XRCC1 Arg194Trp, ERCC4 Arg 415 Gln, ERCC5 Asp1104His in their homozygous wild and heterozygous mutant type. ERCC5 Asp1104His is associated with significant difference in their homozygous mutant type. Total Finger Ridge Count (TFRC<126) is associated with significant difference with all the four DNA repair genes in their homozygous wild and heterozygous mutant type. ATD Angle (<43°) is associated significantly with XRCC3 Thr241 Met in their homozygous wild, heterozygous mutant type and also homozygous mutant type (p<0.05) (Table 1 & Fig 1).

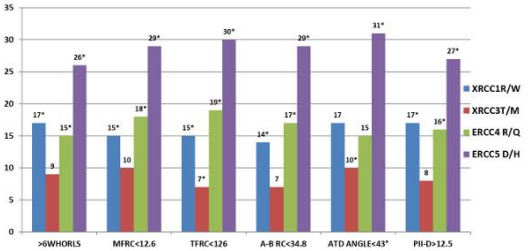
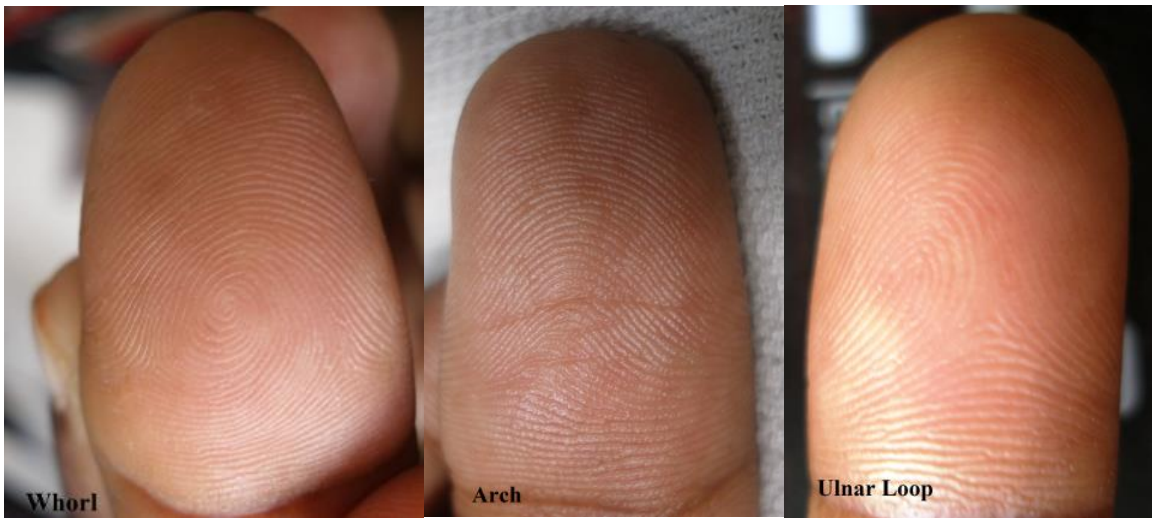


Figure 1: Dermatoglyphic Pattern Frequency Association with Variant Allele of DNA Repair Gene – heterozygous mutant. (*Statistically significant)

On analyzing the risk ratio of breast cancer and high risk group for the dominant pattern of inheritance, it presented the relative risk for six or more whorls around three times for both high risk and breast cancer group respectively for genotypes XRCC1 Arg 194 Trp, ERCC4 Arg 415 Gln, ERCC5 Asp 1104 His with statistically significant difference. The relative risk of MFRC is around 2, even though the risk is presented to be 2 it is not statistically significant. The RR for PII-D is >1 for XRCC1 Arg 194 Trp and ERCC5 Asp 1104 His in breast cancer group and RR is 2 for XRCC1 Arg 194 Trp, ERCC4 Arg 415 Gln, ERCC5 Asp 1104 in high risk group with statistical significance. The RR for A-B RC is 2 for XRCC1 Arg 194 Trp and 3 for ERCC4 Arg 415 Gln in breast cancer group and 2 for ERCC5 Asp 1104 His in high risk group with statistical significance (Table-2).



Figures 2,3,4: Dermatoglyphic Patterns - Whorl, Arch and Ulnar Loop

Table 1: Association between Dermatoglyphics and Polymorphism of DNA Repair Gene.

Gene &Codon	Genotype		Negative and Positive pattern Frequency					
			≥6 Whorls N=63(42)	MFRC <12.6, N= 105(70%)	TFRC, <126, N=100(66)	A-B ridge count <34.8- n=67(45)	ATD angle <43°, n= 123(82%)	PII- D->12.5 N=78(52)
XRCC1 R194W	R/R	OR (CI at 95%)	60.43 (7.90-462.0)	4.14 (1.18 – 14.5)	3.43 (1.11-0.55)	7.62 (2.70-21.5)	15.6 (0.9-255.2)	35.50 (4.6-270.0)
		P Value	**0.0001**	**0.03**	**0.03**	**0.0001**	0.06	**0.0006**
	R/W	OR (CI at 95%)	0.017 (0.002-0.13)	0.25 (0.07-0.89)	0.30 (0.10-0.95)	0.14 (0.04-0.39)	0.06 (0.003-1.1)	0.02 (0.003-0.2)
		P Value	**0.0001**	**0.03**	**0.04**	**0.0002**	0.06	**0.0007**
	W/W	OR (CI at 95%)	0.2 (0.009-5.94)	0.76 (0.03-19.15)	0.65 (0.02-16.4)	0.26 (0.01-6.62)	1.48 (0.05-37.4)	0.35 (0.01-8.88)
		P Value	0.3819	0.87	0.78	0.41	0.81	0.35
XRCC3 T241W	T/T	OR (CI at 95%)	1.77 (0.7-4.06)	0.72 (0.30-1.72)	0.28 (0.12-0.67)	1.09 (0.47-2.48)	0.18 (0.07-0.47)	0.90 (0.39-2.06)
		P Value	0.17	0.46	**0.004**	0.83	**0.0004**	0.81
	T/M	OR (CI at 95%)	0.55 (0.23-1.34)	1.50 (0.60-3.73)	2.84 (1.16-6.92)	0.94 (0.39-2.27)	3.60 (1.37-9.45)	1.10 (0.45-2.63)
		P Value	0.191	0.38	**0.02**	0.90	**0.0009**	0.81
	M/M	OR (CI at 95%)	0.7176 (0.09-5.23)	0.77 (0.07-7.63)	6.31 (0.64-62.3)	0.80 (0.11-5.8)	15.2 (1.5-152.8)	1.08 (0.14-7.91)
		P Value	0.74	0.82	0.11	0.82	**0.02**	0.83
ERCC4 R415Q	R/R	OR (CI at 95%)	8.571 (3.4-21.5)	5.86 (1.69-20.35)	24.1 (3.1-182.5)	16.01 (5.25-48.7)	0.63 (0.25-1.61)	6.16 (2.3-16.01)
		P Value	**<0.0001**	**0.005**	**0.002**	**<0.0001**	0.34	0.94
	R/Q	OR (CI at 95%)	0.1522 (0.06-0.38)	0.20 (0.05-0.72)	0.05 (0.006-0.3)	0.07 (0.02-0.24)	1.52 (0.57-4.02)	0.20 (0.07-0.53)
		P Value	**<0.0001**	**0.01**	**0.003**	**<0.0001**	0.39	**0.0002**
	Q/Q	OR (CI at 95%)	0.075 (0.004-1.46)	0.24 (0.01-4.70)	0.21 (0.01-4.02)	0.08 (0.004-1.5)	1.53 (0.15-15.3)	0.11 (0.006-2.1)
		P Value	0.08	0.35	0.30	0.09	0.71	0.14
ERCC5 D1104H	D/D	OR (CI at 95%)	22.868 (9.254-56.5)	8.63 (2.88-25.83)	24.00 (5.5-104.1)	72.59 (20.3-259)	18.41 (2.4-140.1)	15.81 (6.11-40.8)
		P Value	**0.0001**	**0.0001**	**<0.0001**	**<0.0001**	**0.004**	**<0.0001**
	D/H	OR (CI at 95%)	0.0623 (0.02-0.15)	0.14 (0.04-0.42)	0.05 (0.01-0.22)	0.01 (.005-0.06)	0.06 (0.008-0.4)	0.08 (0.03-0.21)
		P Value	**<0.0001**	**0.0005**	**0.0001**	**<0.0001**	**0.008**	**<0.0001**
	H/H	OR (CI at 95%)	0.06 (0.003-1.12)	0.20 (0.01-3.70)	0.17 (0.009-3.1)	0.06 (0.003-1.2)	0.3 (0.02-7.29)	0.09 (0.005-1.6)
		P Value	**0.05**	0.20	**0.23**	0.07	0.53	0.10

Table 2: Risk Ratio and Odds Ratio of Polymorphism (Dominant Model) In Breast Cancer and High Risk Population with Distinct Dermatoglyphic Pattern.

Dermatoglyphic Variables	Groups	RR/OR/ P -value	XRCC1 Arg194Trp	XRCC3 Thr214Met	ERCC4 Arg415Gln	ERCC5 Asp1104His
≥ six whorls	Breast cancer	RR (95% CI)	3(1.89-4.76)	1(0.45-2.02)	3(1.51-4.05)	3(1.60-4.21)
		OR(95% CI)	∞	1(0.20-4.12)	13(2.48-66.16)	13(3.68-45.8)
		P Value	**<0.0001**	1	**0.0007**	**<0.0001**
	High Risk	RR(95% CI)	3(1.87-4.34)	1(0.72-2.45)	3(1.46-4.31)	3(1.74-6.11)
		OR(95% CI)	∞	2(0.44-7.5)	9.06(2.13-38.49)	15(3.51-66.84)
		P value	**<0.0001**	0.48	**0.002**	**<0.0001**
MFRC <12.6	Breast cancer	RR(95% CI)	2(1.01-1.32)	1(0.53-1.21)	1(1.01-1.34)	1.17(0.96-1.51)
		OR(95% CI)	∞	0.23(0.03-1.67)	∞	7(0.74-70.51)
		P Value	0.30	0.17	0.16	0.14
	High risk	RR(95% CI)	1(0.84-1.40)	1(0.67-1.31)	1(0.72-1.25)	1.22(0.98-1.52)
		OR(95% CI)	1(0.20-17.5)	1(0.11-4.16)	1(0.15-3.60)	5(0.59-46.5)
		P Value	0.67	1	1	0.13
PII>12.5	Breast cancer	RR(95% CI)	1.3(1.13-1.69)	1(0.43-1.30)	1(0.76-1.36)	1.5(1.07-2.25)
		OR(95% CI)	∞	0.33(0.06-1.72)	1(0.24-5.06)	9(1.72-50.61)
		P Value	**0.04**	0.33	1	**0.008**
	High risk	RR(95% CI)	2(1.19-2.45)	1(0.56-1.76)	2(1.24-2.77)	2(1.05-2.57)
		OR(95% CI)	8(0.94-70.4)	1(0.24-4.11)	8(1.54-40.09)	4(1.08-14.80)
		P Value	**0.03**	1	**0.01**	**0.04**
A-B RC <34.8	Breast cancer	RR(95% CI)	2(1.32-3.19)	1(0.31-2.08)	3(1.65-4.26)	∞
		OR(95% CI)	8(1.63-43.17)	0.7(0.15-3.23)	27(3.22-234)	∞
		P Value	**0.0009**	0.71	**0.0001**	3.75
	High risk	RR(95% CI)	1(0.91-1.80)	1(0.46-1.36)	1.3(0.99-1.84)	2(1.32-2.59)
		OR(95% CI)	3(0.51-14)	0.5(0.11-2.13)	4(0.74-19.6)	∞
		P Value	0.30	0.43	0.17	**0.0006**

RR – Risk ratio, OR- Odds ratio

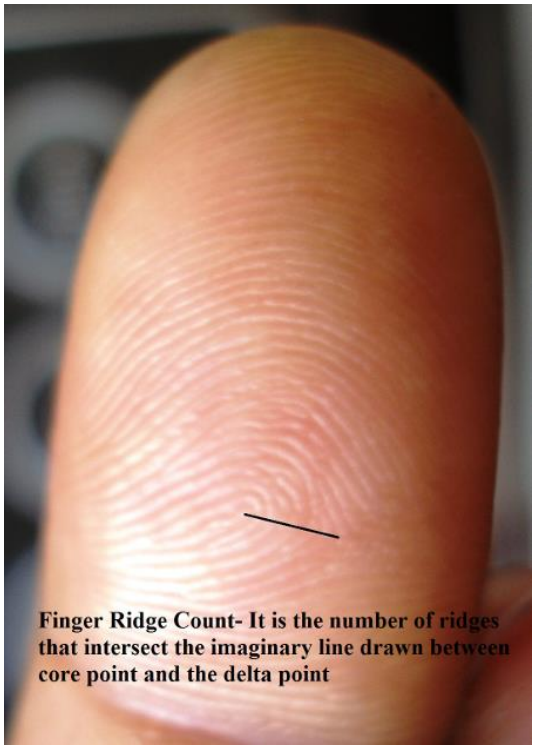


Figure 5: Finger Ridge Count

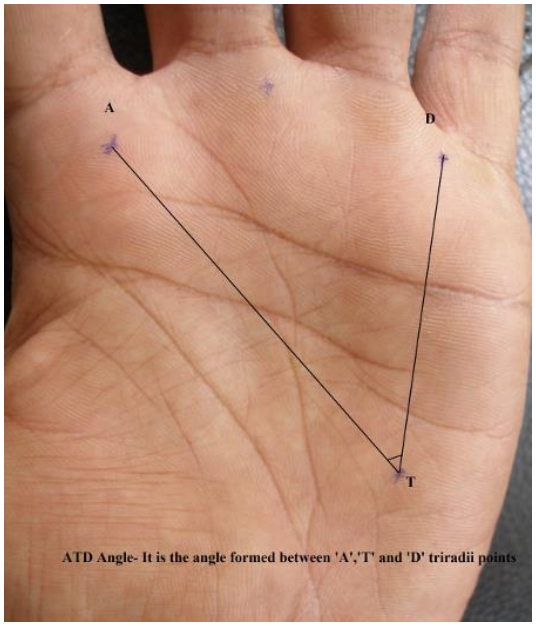


Figure 6: ATD Angle

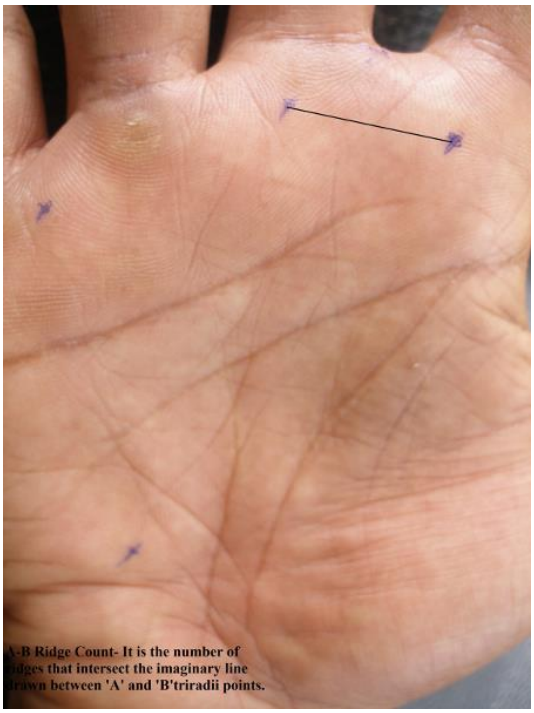


Figure 7: A-B Ridge Count

Discussion:

Of all the genes involved in the process of carcinogenesis, DNA Repair genes forms the corner stone. Instability of DNA Repair gene leads to instability of proto-oncogene, oncogene, tumor suppressor gene and suicidal genes. It has got specific pathways namely NER,BER,HR,DSB which takes important role in repairing the damages caused by aging, exposure to oxidative stress etc., The DNA Repair Gene is the back bone of all the other genes. The four SNP are found to be reported in number of studies to be associated with breast cancer (8-11), which is in agreement with the present study. In observation, three SNPs namely XRCC1 Arg194Trp, ERCC4 Arg 415 Gln, ERCC5 Asp1104His reported to have significant associated with breast cancer and high risk in the present study. The Results of XRCC3 Thr241Met is inconclusive.

On Observation dermatoglyphic variables six and more than six whorls, mean finger ridge count (MFRC<12.6), A-B ridge count (<34.8) and digital pattern intensity index (PII-D >12.5) are observed to be associated in increased frequency with the variant allele of DNA repair gene single nucleotide polymorphism rs1799782, rs1800067 and rs17655 in their heterozygous mutant type and with rs17655 in their homozygous mutant type also. Total finger ridge count (TFRC<126) is observed to be associated in increased frequency with the variant allele of DNA repair gene Single nucleotide polymorphism rs1799782, rs861539, rs1800067 and rs17655 in their heterozygous mutant type alone. ATD Angle (<43°) observed to be associated in increased frequency with the variant allele of DNA repair gene single nucleotide polymorphism rs861539 in their heterozygous mutant type and homozygous mutant type and rs17655 in their hetero mutant type. The relative risk is about 2 to 4 times with statistical significance for breast cancer and high risk group for the genes XRCC1 Arg194Trp, ERCC4 Arg 415 Gln, ERCC5 Asp1104His in their dominant model in both breast cancer and high risk group for the variables six or more whorls, PII-D, A-B RC.

The study of dermal ridge patterns on the skin of palm of hand and sole of foot play a vital role in the field of forensic, anthropology, criminology and medicine.(12) Because of less

number of researches in dermatoglyphics, its role in medical field is very limited. Importance of dermal ridges is still given only in the field of forensic, person identity etc,. The hidden secrets of dermal ridges of skin need to be broken in the field of medicine to be used as a useful, powerful, sensitive, and cost-effective, less time consuming screening, diagnostic procedure. Number of studies reported the association of dermal ridge pattern and breast cancer.(13-18) But still the concept of development of dermal ridges and its genetic base remains unclear. Similarly number of studies reported the genetic basis of breast cancer.(8,10,11) As specific dermatoglyphic parameters are related to breast cancer and both breast cancer and the dermal ridges have the genetic base, it is suggested that there can be a common genetic basis for distinct dermal ridge in relation to breast cancer. Breast cancer is expressed only after getting exposed to inducing factors, but dermal ridges are developed in the womb itself and the status of gene is expressed in the dermal ridges which remains unchanged forever. So even before the process of carcinogenesis begins or the appearance of visible tumor one can be screened for breast cancer risk which aids for effective preventive measures and early therapies and improves the quality of life. To investigate this hypothesis the association of distinct dermal ridges and DNA repair gene SNPs are observed for the first time.

Conclusion

The results of the present study confirmed the involvement of XRCC1 Arg194Trp, ERCC4 Arg 415 Gln, and ERCC5 Asp1104His in breast cancer particularly in population with distinct dermal ridge pattern. It can be suggested the dermal ridges can be used as an effective biomarker of genomic instability in breast cancer. Thus the study aimed to investigate the genetic background of association between breast cancer and distinct palm ridge pattern. It can be suggested that the dermal ridge pattern can be used as a biomarker of specific DNA Repair gene polymorphism that serves as a screening procedure.

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Conflict of interest: Nil

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