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ASSOCIATION OF SINGLE NUCLEOTIDE POLYMORPHISMS OF CDH1 GENE WITH BREAST CANCER: AN IN-SILICO APPRAOCH

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Abstract

Breast cancer, being the second most commonly found form of cancer in females, has become a major focus of research in recent decades. Multiple genes contribute to its incidence. Among these, CDH1 being involved in cell adhesion of epithelial tissues, is reported to have strong association with breast cancer. In current study, coding sequence (CDS) of wild-type CDH1 gene and its seven single nucleotide polymorphisms (SNPs) were retrieved from ENSEMBL database. Mutated CDS were constructed manually. These mutated sequences were analyzed through different tools like PROTPARAM, SOPMA and SWISSMODEL server in order to check the effect of SNPs on physicochemical attributes and secondary (2D) and tertiary (3D) configuration of protein. P160X, T279X and E463 impacted the physical and chemical properties of protein. Lowest number of amino acids. i. e., 213 was contributed by P160X. Considerable variation in pI (10.41 and 8.64) and instability index (46.17 and 42.49) was contributed by these frameshift deletion mutations. These same variants also induced deviation in alpha helix (18 and 17), extended sheet (62 and 86) and random coil (133 and 177) proportions of mutated proteins. All variants altered the 3D configuration of protein particularly P160X and T279X. These SNPs reduced the level of complex folding in mutated forms as compared to the wild type protein. Hence, the frameshift deletion mutations analyzed in current study, P160X and T279X might be recommended as biomarkers for breast cancer as they might play deterministic role for this disease.*

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer which has become a health challenge globally (Wilkinson and Gathani 2022). A recent study revealed that in 2022, 2.3 million new cases and

approximately 670,000 deaths among females due to breast cancer occurred in 185 countries. By 2050, deaths and new cases are expected to increase by 68 and 38 %, respectively (Deng et al. 2025, Kim et al. 2025). This is a multifactorial trait caused by environment as well as genetic factors. Environmental factors include alcohol and tobacco use, diethylstilbestrol (DES) exposure, obesity, use of birth control pills, lack of exercise, aging, previous chest radiation exposure, post-manopausal hormone therapy (PHT), dense breast tissues and more menstrual cycles. Additionally, genes also contribute considerably to the incidence of disease (Fu et al. 2025, Kori 2018).

Breast cancer is a polygenic trait being controlled by several genes including (BRCA1), (BRCA2), partner and localizer of BRCA2 (PALB2), checkpoint kinase 2 (CHEK2), CaDHerin 1 (CDH1), phosphatase and TENsin homolog (PTEN), serine/threonine kinase 11 (STK11), tumor protein p53 (TP53), ataxia telangiectasia mutated (ATM), BRCA1 associated RING domain 1 (BARD1), BRCA 1 interacting protein C-terminal helicase 1 (BRIP1), caspase 8 (CASP8), cytotoxic T-lymphocyte associated protein 4 (CTLA4), cytochrome p450 family 19 subfamily A member 1 (CYP19A1), H10 imprinted maternally expressed transcript (H19), lymphocyte-specific protein 1 (LSP1), mitogen activated protein kinase 1 (MAP3K1),meiotic recombination 11 homolog A (MRE11A), nibrin (NBN), DNA repair protein (RAD51), telomerase reverse transcriptase (TERT), cadherin 1 (CDH1), fibroblast growth factor receptor 2 (FGFR2), MutS homolog 6 (MSH6) (Afzaljavan et al. 2023, Barros-Oliveira et al. 2020, Chen et al. 2022, Costa et al. 2020, da Silva et al. 2021, Elkholi et al. 2021, Hsu et al. 2020, Kern and Panis 2021, Li Cheukfai et al. 2022, Li Feifei et al. 2021, Moyer et al. 2020, Rainville et al. 2020, Santolla and Maggiolini 2020, Shahbandi et al. 2020, Śniadecki et al. 2020, Stucci et al. 2021, Vaidyanathan and Kaklamani 2021, Wang et al. 2020, Wu et al. 2020, Xie et al. 2022, Zuntini et al. 2021).

Among these genes, CDH1 has strong association with hereditary lobular breast cancer (HLBC). Under normal circumstances this gene plays role in adhesion of tissue epithelial cells as it encodes epithelial cadherin protein (Ku et al. 2022). Any mutation in this gene may result in cell adhesion disruption and loss of normal structure and function of breast tissue (Garcia-Pelaez et al. 2023). Literature documented various mutations in CDH1 gene in breast cancer patients (Adib et al. 2022, Corso et al. 2020).

Keeping in view, this association of CDH1gene with breast cancer, we initiated current research project aiming at identifying the CDH1 gene associated variants. These variants might be tested for their impact on different attributes of encoded protein. Those with considerable effects might be used as prognostic and diagnostic biomarkers for this disease.

2. Methodology

2.1 Retrieving the coding sequence (CDS) and SNPs data from database

CDH1 gene transcript (ENST00000261769.10) comprising of 4811bp was selected for characterization. This transcript encodes protein comprising of 882 amino acids. The coding sequence (CDS) and SNPs of this transcript were retrieved from ENSEMBL genome browser (https://www.ensembl.org/index.html, accessed on January 2025) (Zerbino et al. 2018)33. Total seven SNPs including three missense, one stop gained and three frameshift deletion mutations were selected (Table 1). Selection of missense SNPs was based on their deleterious status that was computed through SIFT and PolyPhen tools.

Table 1: SNPs of CDH1 gene documented in current study, their consequences type, codon position, nucleotide and codon change and deleteriousness score predicted by SIFT and PolyPhen

Case ID	SNP ID	Consequence type	Codon position	Nucleotide change	Codon change	SIFT	PolyPhen
G31C	rs2152114387	missense	31	GGC>TGC	G > C	0	0.964
P160X	rs2152129745	frameshift deletion	160	CCC>CC	P > X	~	~
T279X	rs1960834407		279	ACC>AC	T > X	~	~
F375C	rs1960860209	Missense	375	TTC>TGC	F > C	0	1
E463*	rs1960961009	Stop gained	463	GAG>TAG	E > *	~	~
C695W	rs1596965954	missense	695	TGT>TGG	C > W	0	1
G715X	rs1555517153	Frameshift deletion	715	GGA>GA	G > X	~	~

2.2 Construction of mutated CDS and Expasy Translate tool

After CDS retrieval, the sequence was organized into codons manually. To construct the mutated CDS, required nucleotide change for each variant was inserted at the specific codon position in the CDS of wild type sequence (Supplementary Data Figure S1). Afterwards, wild type and mutated CDS were translated into amino acids sequence using Expasy Translate tool (Supplementary Data Figure S2) (https://web.expasy.org/translate/, accessed on January 2025).

2.3 PROTPARAM

Expasy PROTPARAM tool (https://web.expasy.org/protparam/, accessed on January 2025) was employed in order to compute the effect of mutations on mutated proteins physical and chemical features (Garg et al. 2016). The attributes analyzed were number of amino acids, molecular weight, isoelectric point (pI), instability and aliphatic index.

2.4 SOPMA

SOPMA protein secondary (2D) structure prediction tool (available at https://npsa.lyon.inserm.fr/cgi-bin/npsa_automat.pl?page=/NPSA/npsa_sopma.html, accessed on January 2025) which is accessible at NPS@: Network Protein Sequence @nalysis was employed to check the effect of mutations on encoded protein. Three attributes of 2D configuration. i. e., alpha helix, extended sheet and random coil, were assessed. Three parameters considered for analysis were window width (17), number of states (3) and similarity threshold (8) (Geourjon and Deleage 1995).

2.5 SWISSMODEL server

To predict the effect of mutations on 3D configuration of mutated proteins, SWISSMODEL server (https://swissmodel.expasy.org, accessed on January 2025) was accessed (Schwede et al. 2003). The parameters of GMQE score and sequence identity were computed.

To validate the structures of wild type and mutated proteins generated through SWISSMODEL server, Ramachandran plots were constructed through the same platform. Attributes of structures like the morbidity and clash scores, Ramachandran favoured region and outliers, rotamer outliers and C-beta deviations were predicted.

3. Results

3.1 Assessment of effect of SNPs on physicochemical properties of mutated proteins

All the SNPs except G31C, F375C and C695W were found to alter the physical and chemical attributes of mutated proteins considerably (Table 2). Highest deviation from number of amino acids and molecular weight of wild type protein was observed in case of P160X. i. e., 213 and 24385.11, respectively followed by T279X, E463* and G715X. P160X caused significant increase in pI (10.41) as compared to wild type value of 4.57, followed by T279X (8.64) and E463* (5.30). Only SNPs P160X and T279X caused alteration in aliphatic index values. i. e., 74.60 and 75.46, respectively.

Table 2: Assessment of impact of CDH1 gene SNPs on physicochemical properties of mutated proteins based on PROTPARAM tool

SNP case	No. of amino acids	Molecular weight	pI	Instability index	Aliphatic index
Wild type	882	97456.15	4.57	35.42	84.54
G31C	882	97502.24	4.57	35.34	84.54
P160X	213	24385.11	10.41	46.17	74.60
T279X	280	31571.87	8.64	42.49	75.46
F375C	882	97412.12	4.57	35.43	84.54
E463*	462	51097.49	5.30	32.26	80.11
C695W	882	97539.23	4.57	35.43	84.54
G715X	720	79433.40	4.75	31.00	84.58

3.2 Assessment of effect of SNPs on secondary (2D) configuration of mutated proteins

SOPMA tool helped to predict the impact of seven SNPs on 2D structure of mutated proteins. All the SNPs altered the structure considerably, however, SNPs G31C, F375C and C695W caused slight change. SNPs P160X, T279X, G715X and E463* impacted the 2D structural attributes considerably (Table 3 and Figure 1). Highest deviation of alpha helix content as compared to wild type value (91) was observed in T279X (17). SNP P160X considerably altered the extended sheet content. i. e., 62 versus wild type content of 264. In case of random coil, maximum deviation from normal value of 527 was observed to be caused by P160X. i. e., 133.

Table 3: Assessment of impact of CDH1 gene associated SNPs on secondary (2D) configuration of encoded mutated proteins based on SOPMA tool

Case ID	Alpha helix (%)	Extended sheet (%)	Random coil (%)
wild type	91 (10.32)	264 (29.93)	527 (59.75)
G31C	82 (9.30)	259 (29.37)	541 (61.34)
P160X	18 (8.45)	62 (29.11)	133 (62.44)
T279X	17 (6.07)	86 (30.71)	177 (63.21)
F375C	85 (9.64)	268 (30.39)	529 (59.98)
E463*	24 (5.19)	155 (33.55)	283 (61.26)
C695W	80 (9.07)	274 (31.07)	528 (59.86)
G715X	33 (4.58)	254 (35.28)	433 (60.14)

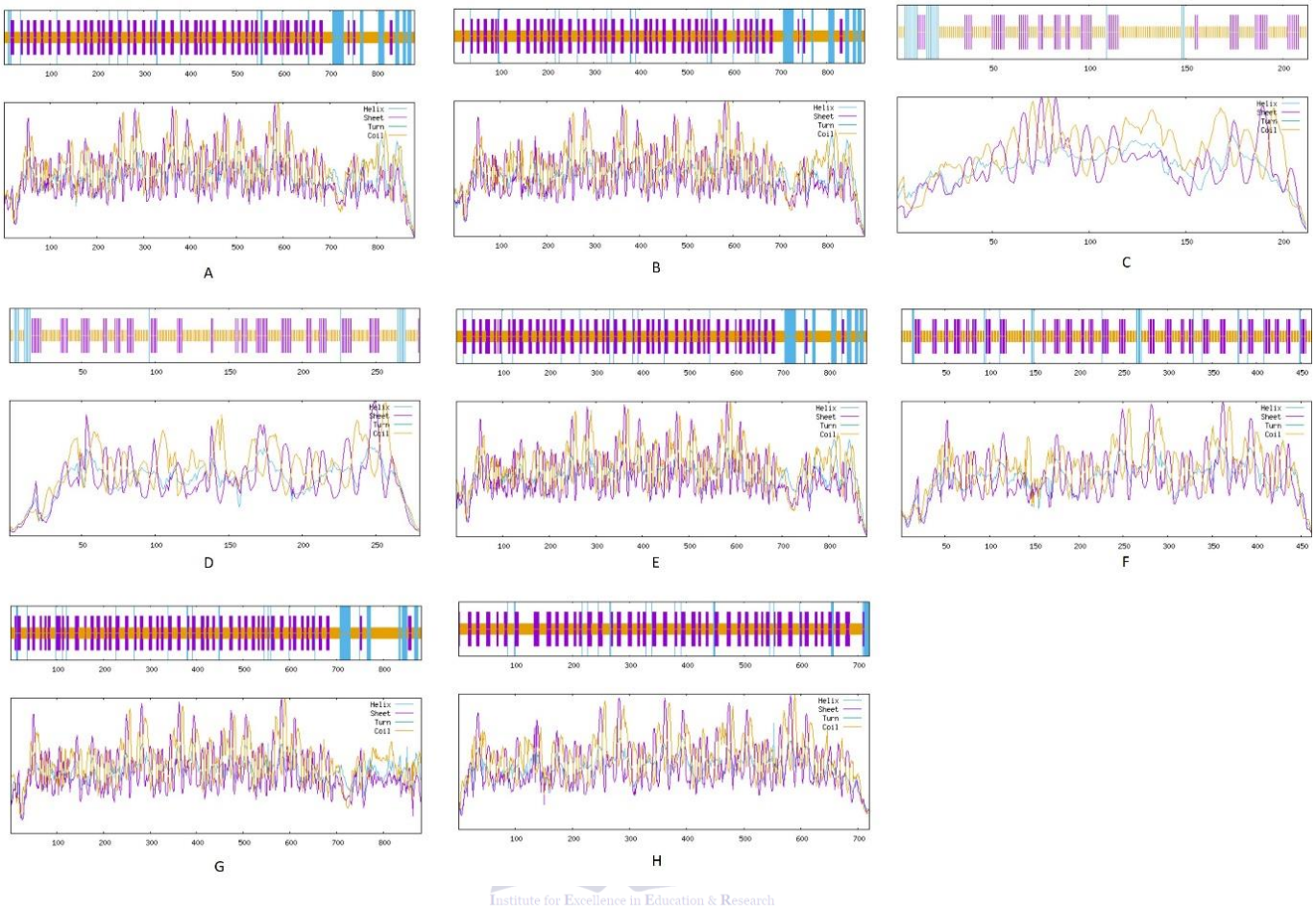

Figure 1: Analysis of impact of CDH1 gene associated SNPs on 2D configuration of encoded mutated protein through SOPMA tool
A: wild type, B: G31C, C: P160X, D: T279X, E: F375C, F: E463*, G: C695W, H: G715X

3.3 Assessment of effect of SNPs on three dimensional (3D) configuration of mutated proteins
All the mutated cases demonstrated structural variations from wild type form. SNPs in cases P160X and T279X considerably reduced the complexity of 3D structure of mutated proteins. Impact of F375C and G715X on mutated proteins was found same (Figure 2). In wild-type protein structure, the GMQE value was 0.80 and sequence identity was predicted as 98.30%. In case G31C, GMQE score was 0.80 and sequence coverage was 98.19%. In P160X, the GMQE was 0.70 and sequence identity was 81.25 %. In T279X, GMQE value and sequence identity were observed as 0.77 and 98.92 %, respectively. In F375C, the GMQE value was found as 0.85 with 100% sequence identity. In E463*, GMQE value was 0.84 with 98.48% sequence identity. In C695W, the GMQE score was 0.80 and sequence identity was found as 98.19%. In G715X, the GMQE and sequence identity predicted were 0.85 and 100%, respectively.

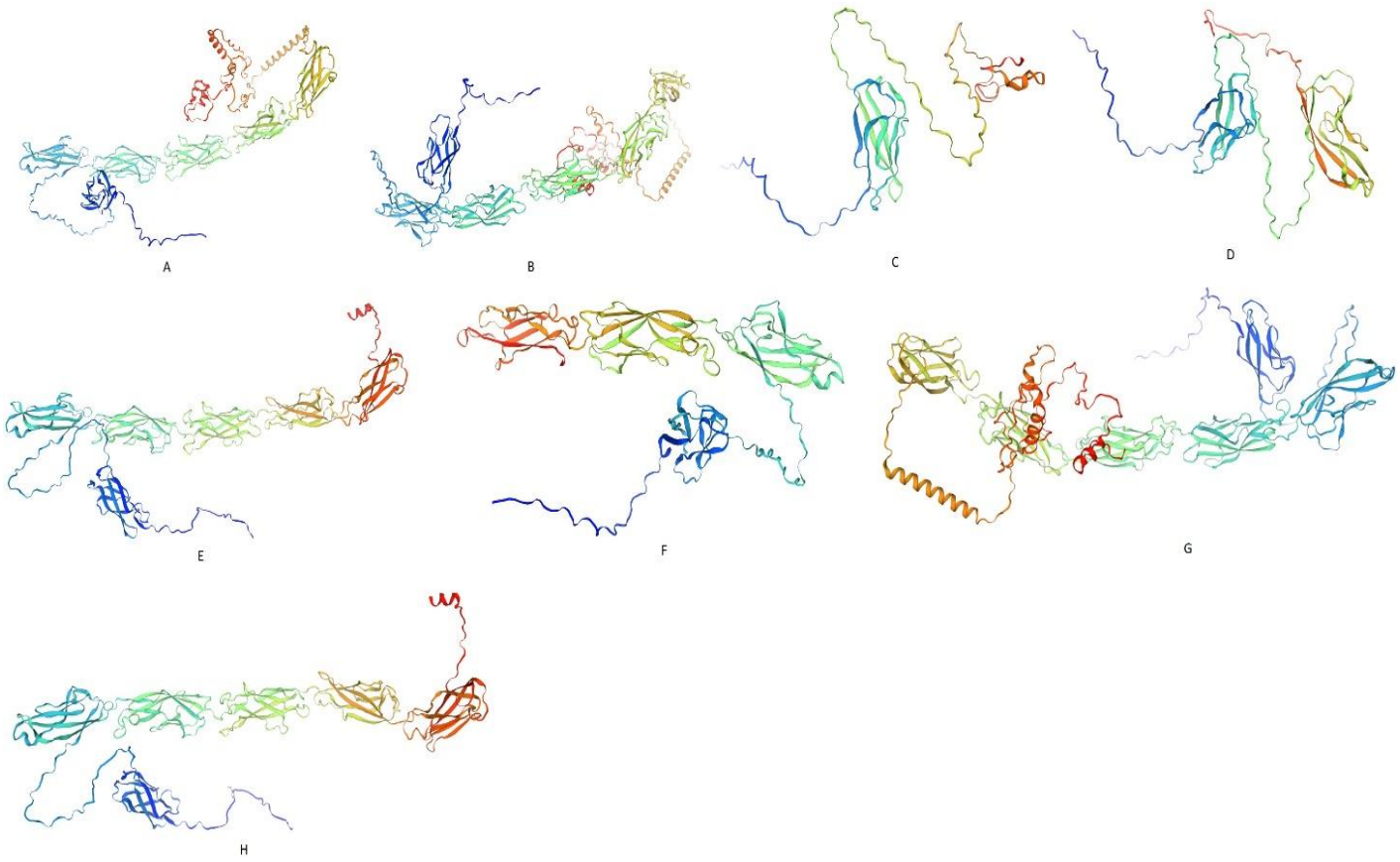

Figure 2: Assessment of impact of CDH1 gene associated SNPs on 3D configuration of mutated proteins based on SWISSMODEL server
A: wild type, B: G31C, C: P160X, D: T279X, E: F375C, F: E463*, G: C695W, H: G715X

3.4 Validation of 3D configurations

In case of wild-type protein, the MolProbity score was 1.60 and clash score was 0.44. Ramachandran favoured and outliers were 90.57 and 2.61%, respectively. The rotamer outliers were 3.51%. C-beta deviations were 15. In case G31C, morbidity and clash scores were 1.61 and 0.44, respectively. Ramachandran favoured and outliers were predicted as 90.45 and 2.73 %, respectively. Rotamer outliers were 3.51 % and 15 C-beta deviations were observed. In case of P160X, the morbidity and clash score, Ramachandran favoured and outliers, rotamer outliers and C-beta deviations were found as 2.02, 1.17, 86.47 %, 7.25 %, 5.35 % and 9, respectively. In T279X, the morbidity and clash score, Ramachandran favoured and outliers, rotamer outliers and C-beta deviations were predicted as 1.71, 0.45, 90.61%, 4.69 %, 4.84 % and 8, respectively. In F375C and G715X, the morbidity and clash score, Ramachandran favoured and outliers, rotamer outliers and C-beta deviations were predicted as 1.37, 0.46, 92.42%, 2.25%, 2.08% and 13, respectively. In E463*, the scores of morbidity and clash were predicted as 1.50 and 0.42, respectively. 93.26 was the percentage of favoured region. 2.83% were Ramachandran outliers. The rotamer outliers were observed as 3.46% with 10 C-beta deviations. In C695W, the morbidity and clash score, Ramachandran favoured and outliers, rotamer outliers and C-beta deviations were predicted as 1.60, 0.44, 90.34%, 2.73%, 3.38% and 9, respectively (Figure 3).

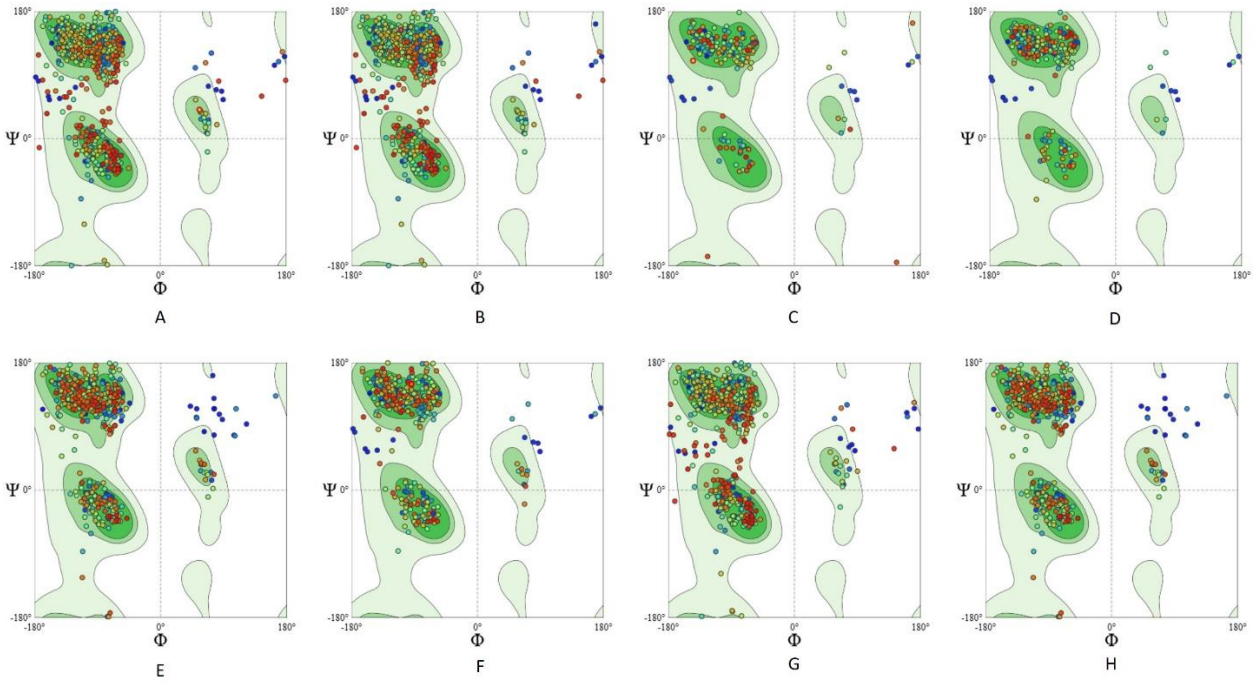

Figure 3: Validation of 3D structures of wild type and mutated proteins through Ramachandran plots constructed via SWISS-MODEL server
A: wild type, B: G31C, C: P160X, D: T279X, E: F375C, F: E463*, G: C695W, H: G715X

4. Discussion

Several mutations of CDH1 gene have been documented in previously published literature that are associated with breast cancer like rs3743674, -16C/A polymorphism, rs13689, rs7198799, rs7200690, rs17715799, rs13689, rs12185157, rs7200690, rs7198799 and A617T (Jia et al. 2015, Lajus and Sales 2015, Ma et al. 2016, Rahim et al. 2022, Sirisena et al. 2018). However, this is the first ever study documenting the association analysis of rs2152114387, rs2152129745, rs1960834407, rs1960860209, rs1960961009, rs1596965954 and rs1555517153 SNPs.

Instability index indicate the stability of protein (Gamage et al. 2019). Five variants cases G13C, F375C, E463*, C695W and G715X conferred greater stability to mutated proteins while two cases P160X and T279X decreased stability by increasing instability index value above 40. The aliphatic index is a measure of thermal stability of proteins (Xiao and Chou 2007). In current investigation all the SNPs caused no change in thermal stability of mutated proteins. However, P160X and T279X slightly lower the value of aliphatic index.

Three variants. i. e., P160X, T279X and E463* significantly reduced the proportion of amino acids taking part in formation of alpha helix, extended sheet and random coil of mutated proteins. As alpha helix and extended sheets contribute to stability of proteins and random coil confers flexibility to protein during its interaction with legends (Berjanskii and Wishart 2008, Pauling 2015, Yu 2005). So, these three variants markedly reduce the stability and interacting potential of mutated proteins.

According to current study findings, two SNPs rs2152129745 and rs1960834407 documented in cases P160X and T279X, respectively, conferred lower stability to mutated proteins and reduced the folding in 3D structure. These two variants might be recommended for experimental validation in future perspectives of this study.

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