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Investigation of PAX8 Gene Associated Biomarkers of Cervical Cancer through In-Silico Analysis

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Abstract
Globally, cervical cancer is the fourth most prevalent cancer among human females. This cancer is caused by human papillomavirus (HPV) regulated aberrant expression of various proliferation associated genes like PAX8. Current study has focused the susceptibility status of PAX8 gene variants for cervical cancer. For this study, coding sequence (CDS) and seven SNPs of PAX8 gene were retrieved from ENSEMBL database. Mutated CDS were prepared and analyzed via SOPMA tool, SWISSMODEL server and MEME suite. The alpha helix and random coil components of secondary (2D) structure and tertiary (3D) folding complexity were greatly reduced by SNPs L153X and R207*. Extended strand content was increased by D273Y, S337X, Y400X, S435* and T445M. Only mutation that altered the conserved protein motifs composition of protein as compared to wild type form domains, was L153X. Hence, two variants L153X and R207* might be recommended as biomarkers for prognosis and diagnosis of cervical cancer.

Keywords: cervical cancer, human papillomavirus, biomarkers, PAX8, variants

1. Introduction
In Pakistan, cervical cancer is the third most common cancer among females (Qamar et al. 2025). According to an estimate, in 2018, total number of cases of

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cervical cancer and deaths were 570,000 and 311,000, respectively (Arbyn et al. 2020). Another investigation documented 604127 and 341831 as the number of its cases and deaths, globally in 2020 (Singh et al. 2023). World Health Organization (WHO) has set measurable goals with respect to diseases like cervical cancer under the name "Elimination as a public health problem" which is supported by various societies including International Gynecologic Cancer Society (IGCS) and European Society of Gynaecologic Oncology (ESGO) (Gultekin et al. 2020). An increasing trend of incidence and deaths associated with this cancer has been reported in countries with high alcohol consumption and low to medium human development index (HDI) (Huang et al. 2022).

Major risk factor of cervical cancer is Human papillomavirus virus (HPV), it is transmitted through sexual contact. Other risk factors include family history, reduced immunity, smoking, prolonged use of steroids and socioeconomic factors (Ambad et al. 2024, Oringtho et al. 2024). About 27-36% risk variation of cervical cancer is contributed by genetic factors (Leo et al. 2017). Several genes have been documented with cervical cancer susceptibility variants like tumor protein (p53), mouse double minute 2 homolog (MDM2), ataxia-telangiectasia (ATM), BRCA1 interacting protein C-terminal helicase-1 (BRIP1), cyclin dependent kinase inhibitor 1A (CDKN1A), cyclin dependent kinase inhibitor 2A (CDKN2A), fanconi anemia complementation group C (FANCC), fanconi anemia complementation group C (FANCA), fanconi anemia complementation group L (FANCL), X-ray repair cross complementing 3 (XRCC3), X-ray repair cross complementing 1 (XRCC1), transforming growth factor beta 1 (TGFB1), caspase recruitment domain family member 8 (CARD8), cytotoxic T-lymphocyte associated protein 4 (CTLA4), cluster of differentiation 83 (CD83), interferon gamma (IFNG) and paired box 8 (PAX8) (Alsbeih et al. 2013, Hu et al. 2010, Jin 2015, Juko-Pecirep et al. 2011, Kim et al. 2008, Liu et al. 2017, Ma et al. 2013, Martinez-Nava et al. 2016, Oliveira et al. 2012, Ramachandran and Dörk 2021, Thakur et al. 2012, Yin et al. 2015, Zhang et al. 2007).

Several cervical cancer susceptibility mutations have been documented in literature including rs4848320, rs10175462 and rs1110839 (Bowden et al. 2021, Han et al. 2016). Considering the association of PAX8 gene with cervical cancer, we designed current study to explore the susceptible mutations of PAX8 gene that might be exploited as diagnostic and prognostic biomarkers for this cancer.

2. Methodology

Transcript variant ENST00000429538.8 of gene PAX8, was selected for current study. This transcript comprises of 4055 bp and encodes for 450 amino acids.

2.1 Retrieval of coding sequence and SNPs: ENSEMBL database

The coding sequence (CDS) and single nucleotide polymorphisms (SNPs) of the transcript of PAX8 gene were retrieved from ENSEMBL database (accessed on January 2025, available at https://www.ensembl.org/index.html) (Chen et al. 2010). Total seven SNPs were selected. Among these, three were frameshift deletion, two were stop-gained and two were missense mutations (Table 1). Mutated CDS was designed through incorporation of SNPs in wild type CDS by replacing the normal nitrogenous base with the mutated one.

Dialogue Social Science Review (DSSR)
www.thedssr.com

ISSN Online: 3007-3154
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DIALOGUE SOCIAL SCIENCE REVIEW

Vol. 3 No. 8 (August) (2025)

2.2 EXPASY TRANSLATE TOOL

Both the wild type and mutated CDS were translated into amino acid sequences through EXPASY TRANSLATE TOOL (accessed on January 2025, available at https://web.expasy.org/translate/) (Tools et al. 2010). These sequences were used as input data for the tools that were employed for analysis of SNPs on mutated proteins.

2.3 SOPMA TOOL

SOPMA TOOL (accessed in January 2025, available at https://npsa.lyon.inserm.fr/cgi-bin/secpred_sopma.pl) was consulted to determine the effect of SNPs on mutated proteins secondary (2D) configuration (Geourjon and Deleage 1995). Number of conformational states chosen were four (helix, sheet, turn and coil). The default parameters of output width (70), window width (17) and similarity threshold (8) were used. Amino acid sequence was given as input.

Table 1: SNPs associated with PAX8 gene, their consequence type, codon position, nucleotide change, codon change and SIFT deleterious score, documented in current study

SNP case	SNP ID	Consequence type	Codon position	Nucleotide change	Codon change	SIFT
L153X	rs1690965885	Frameshift deletion	153	CTG > G	L > X	--
R207*	rs1690856985	Stop gained	207	CGA>TGA	R > *	--
D273Y	rs757960433	missense	273	GAC>TAC	D > Y	0
S337X	rs1558700308	Frameshift deletion	337	TCC>TC	S > X	--
Y400X	rs1689194381		400	TAC>TA	Y > X	--
S435*	rs749184183	Stop gained	435	TCA>TGA	S > *	--
T445M	rs746547401	missense	445	ACG>ATG	T > M	0

2.4 SWISSMODEL SERVER

SWISSMODEL server (accessed on January 2025, available at https://swissmodel.expasy.org) was consulted to demonstrate how the variants of current study effected the three dimensional (3D) configuration of mutated proteins (Waterhouse et al. 2018).

3. Results

3.1 Prediction of SNPs effect on 2D structure

Analysis performed through SOPMA tool demonstrated the impact of variants on 2D structure of mutated proteins (Table 2 and Figure 1).

Table 2: Effect of SNPs of PAX8 gene on secondary (2D) configuration of mutated proteins predicted via SOPMA TOOL

Dialogue Social Science Review (DSSR)
www.thedssr.com

ISSN Online: 3007-3154
ISSN Print: 3007-3146

DIALOGUE SOCIAL SCIENCE REVIEW

Vol. 3 No. 8 (August) (2025)

SNP case	Alpha helix	Extended strand	Beta turn	Random coil
Wild type	80 (17.78)	8 (1.78)	21 (4.67)	341 (75.78)
L153X	59 (29.80)	9 (4.55)	0 (0.00)	130 (65.66)
R207*	56 (27.18)	8 (3.88)	23 (11.17)	119 (57.77)
D273Y	78 (17.33)	13 (2.89)	21 (4.67)	338 (75.11)
S337X	80 (18.87)	14 (3.30)	21 (4.95)	309 (72.88)
Y400X	75 (17.69)	13 (3.07)	21 (4.95)	315 (74.29)
S435*	69 (15.90)	11 (2.53)	21 (4.84)	333 (76.73)
T445M	79 (17.56)	20 (4.44)	21 (4.67)	330 (73.33)

The number without brackets is showing the number of amino acids while number given in brackets is representing the percentage of amino acids, taking part in formation of specific portion of 2D configuration

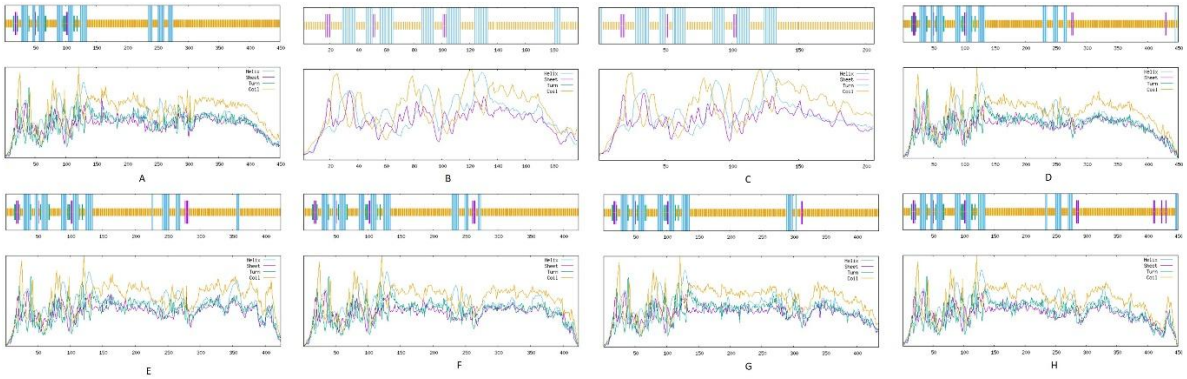

Figure 1: Analysis of impact of SNPs of PAX8 gene on secondary (2D) configuration of mutated proteins

A: wild type, B: L153X, C: R207*, D: D273Y, E: S337X, F: Y400X, G: S435*, H: T445M

Marked deviation from wild type alpha helix (80) was introduced by SNPs L153X (59), R207* (56) and S435* (69). Five mutations. i. e., D273Y (13), S337X (14), Y400X (13), S435* (11) and T445M (20) altered the extended strand value. Only SNP that effected the beta turn normal value (21) considerably was R207* (0). Only two mutations (L153X and R207*) altered the random coil content from 341 for wild type to 130 and 119 for L153X and R207*, respectively.

3.2 Prediction of SNPs effect on 3D configuration

Wild type protein structure was obtained with GMQE and coverage of 0.57 and 99.78%, respectively (Figure 2).

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ISSN Print: 3007-3146

DIALOGUE SOCIAL SCIENCE REVIEW

Vol. 3 No. 8 (August) (2025)

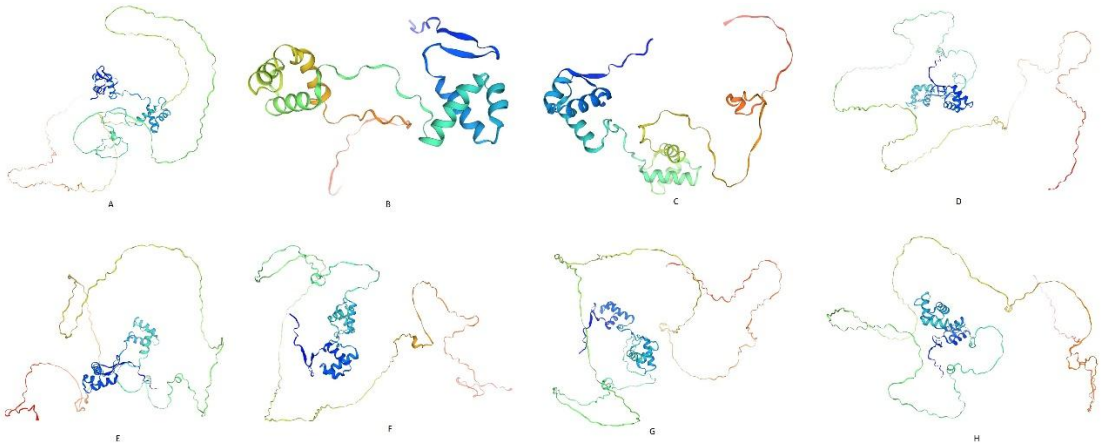

Figure 2: Analysis of impact of SNPs of PAX8 gene on tertiary (3D) configuration of mutated proteins

A: wild type, B: L153X, C: R207*, D: D273Y, E: S337X, F: Y400X, G: S435*, H: T445M

In L153X case, structure was predicted with 0.69 GMQE score and 91.81% sequence identity. In case R207*, structure was found with 0.76 GMQE score and coverage of 100%. In case D273Y, GMQE score and sequence identity were found as 0.57 and 99.56%, respectively. In case of S337X, we found GMQE score of 0.53 and sequence identity of 90.39%. GMQE score of 0.57 and coverage of 96.45% was obtained in case Y400X. GMQE score (0.57) and sequence coverage (99.77%) was identified in case S435*. In case T445M, we found 0.57 GMQE score and 99.56% sequence coverage. All the SNPs caused variation in folding pattern of polypeptide chains but only variants L153X and R207*, reduced the level of complexity of configuration.

3.3 Prediction of SNPs effect on conserved domains of proteins

In variant L153X case, four conserved motifs WQRQEE, LGRYYE, HLLHQW and DLAHQG were identified which were different from those found in wild type protein sequence. R207* did not cause any change in sequences of motifs of mutated protein. In D273Y, two motifs WWQEVN and WWGPRC were different from wild type protein. In Y400X, two domains KRKMDD and NSTLDD were found non-identical with wild type protein. Three motifs. i. e., NAFPHA, NAYGHT and MAFDHL were identified different from wild type sequences (Table 3).

Table 3: Assessment of effect of SNPs of PAX8 gene on the conserved protein motifs of mutated proteins

#	E-value	p-value	Motif
Wild type			
1	9.9e-001	3.32e-24	KPKVATP EKIGDYKRQNPTMF DRLLAEG KVV AWEIR VCD

Dialogue Social Science Review (DSSR)
www.thedssr.com

ISSN Online: 3007-3154
ISSN Print: 3007-3146

DIALOGUE SOCIAL SCIENCE REVIEW

Vol. 3 No. 8 (August) (2025)

2		4.04e-20	NDTVPSV NRIIRTKVQQPFNLP VATKSLSP SSI MDSC GH
3	3.6e+001	6.37e-9	FSQHHLEPLE CPFERQ HYPEAYASPS
4		6.11e-8	VDLAHQGVRP CDISRQ LRVSHGCVSK
5	4.4e+001	7.44e-9	NAYGHTPYSS YSEAWR FPNSSLLSSP
6		3.81e-7	PLECPFERQH YPEAYA SPSHTKGEQG
L153X			
7	2.3e+000	4.77e-16	TPKVVEKIG YKRQNPTMFA IRDRLLAEG D WE V
8		8.39e-14	SVSSINRII TKVQQPFNLPM SCVATKSES R D R
9	8.7e+001	3.24e-8	HQWAPGHRSA WQRQEE NG
10		2.14e-7	RVSHGCVSKI LGRYYE TGSIRPGVIG
11	1.1e+002	2.01e-8	GVTPVGFPGL HLLHQW APGHRSAWQR
12		8.41e-8	LPEVVRQRIV DLAHQG VRPCDISRQL
R207*			
13	1.1e+000	2.18e-22	KPKVATP EKIGDYKRQNPTM IRDRLLA KVV FAWE EGV
14		2.11e-18	NDTVPSV NRIIRTKVQQPFNL SCVATKSL SSI PMD SP
15	3.5e+001	6.20e-9	FSQHHLEPLE CPFERQ HYPEAYASPS
16		6.24e-8	VDLAHQGVRP CDISRQ LRVSHGCVSK
17	5.9e+001	7.85e-9	NAYGHTPYSS YSEAWR FPNSSLLSSP
18		3.98e-7	PLECPFERQH YPEAYA SPSHTKGEQG
D273Y			
19	5.6e-001	4.96e-9	AAMPPLPSQA WWQEVN TLAMPMATPP
20		7.62e-9	RARPSSQGER WWGPRC PDTHPTSPPA
21	5.0e+000	9.21e-21	KPKVATPK EKIGDYKRQNPTM EIRDRLLA VV FAW EG
22		4.81e-17	NDTVPSVS NRIIRTKVQQPFN DSCVATKS SI LPM LS
23	9.1e+000	2.62e-11	QHHLEPLECP FERQHYPE AYASPSHTKG

Dialogue Social Science Review (DSSR)
www.thedssr.com

ISSN Online: 3007-3154
ISSN Print: 3007-3146

DIALOGUE SOCIAL SCIENCE REVIEW

Vol. 3 No. 8 (August) (2025)

24		8.68e-10	SGPRKHLRTD AFSQHHLE PLECPFERQH
S337X			
25	5.6e-001	4.96e-9	AAMPPLPSQA WWQEVN TLAMPMATPP
26		7.62e-9	RARPSSQGER WWGPRC PDTHPTSPPA
27	5.0e+000	9.21e-21	KPKVATPK VV EKIGDYKRQNPTM FAW EIRDRLLA EG
28		4.81e-17	NDTVPSVS SI NRIIRTKVQQPFN LPM DSCVATKS LS
29	9.1e+000	2.62e-11	QHHLEPLECP FERQHYPE AYASPSHTKG
30		8.68e-10	SGPRKHLRTD AFSQHHLE PLECPFERQH
Y400X			
31	4.9e-001	2.15e-24	KPKVATP KVV EKIGDYKRQNPTMF AWEIR DRLLAEG VCD
32		1.16e-19	NDTVPSV SSI NRIIRTKVQQPFNLP MDSC VATKSLSP GH
33	4.8e+001	8.37e-9	FSQHHLEPLE CPFERQ HYPEAYASPS
34		8.69e-8	VDLAHQGVRP CDISRQ LRVSHGCVSK
35	5.2e+002	2.14e-9	LLGIAQPGSD KRKMDD SDQDSCRLSI
36		1.03e-6	EQGLYPLPLL NSTLDD GKATLTPSNT
S435*			
37	1.2e+000	4.50e-24	KPKVATP KVV EKIGDYKRQNPTMF AWEIR DRLLAEG VCD
38		3.73e-20	NDTVPSV SSI NRIIRTKVQQPFNLP MDSC VATKSLSP GH
39	3.6e+001	4.46e-9	FSQHHLEPLE CPFERQ HYPEAYASPS
40		8.89e-8	VDLAHQGVRP CDISRQ LRVSHGCVSK
41	4.1e+001	8.53e-9	NAYGHTPYSS YSEAWR FPNSSLLSSP
42		3.24e-7	PLECPFERQH YPEAYA SPSHTKGEQG
T445M			
43	1.4e+000	2.36e-22	KPKVATP KVV EKIGDYKRQNPTM FAWE IRDRLLA EGV
44		2.30e-18	NDTVPSV SSI NRIIRTKVQQPFNL PMD SCVATKSL SP

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www.thedssr.com

ISSN Online: 3007-3154
ISSN Print: 3007-3146

DIALOGUE SOCIAL SCIENCE REVIEW

Vol. 3 No. 8 (August) (2025)

45	2.1e+001	6.37e-9	FSQHHLEPLE CPFERQ HYPEAYASPS
46		6.03e-8	VDLAHQGVRP CDISRQ LRVSHGCVSK
47	4.2e+001	4.62e-8	QQVGSGVPPF NAFPHA ASVYGQFTGQ
48		3.17e-7	GMVAGSEYSG NAYGHT PYSSYSEAWR
49		3.77e-7	SRPSAPPTTA MAFDHL

4 Discussion

The PAX8 protein, due to its upregulation in tumor cells, is associated with cervical cancer. It confers infinite proliferation potential to tumor cells (Chaves-Moreira 2021). Additionally, this gene demonstrated rearrangements and abnormal transcripts production in cervical cancer cells (López-Urrutia et al. 2016). Over-expression of PAX8 in cancer cells regulates the expression of p53, p21, E2F1 and Bcl2 resulting in uncontrollable cell division (Khizer et al. 2021). Expression of this gene is enhanced in case of HPV positive lesions (Ramachandran and Dörk 2021).

Conserved motifs are the sequences within family of proteins which indicate the binding sites for enzymes like transcription regulators and DNA and RNA. These sites also regulate the folding patterns of proteins (Ren et al. 2008). In current study, six conserved domains were found in wild type protein EKIGDYKRQNPTMFAWEIR, NRIIRTKVQQPFNLPMDSC, CPFERQ, CDISRQ, YSEAWR and YPEAYA. These domains were also found in some of the mutated proteins but some were absent in response to polymorphism like L153X, D273Y, S337X, Y400X and T445M. This finding is suggesting that these mutated proteins might interact differently with their binding partners resulting in alteration of protein function. This is the first study predicting effects of PAX8 gene on the conserved motifs of encoded proteins.

Alpha helix contributes to overall stability of protein due to inherent hydrogen bonds. L153X and R207* are the only variants reducing the stability of mutated proteins (Pauling 2015). L153X also decreased the random coil and beta turn contents of protein. These two SNPs also reduced the degree of complex folding in protein. Among the variants documented in current study, L153X and R207* might be tested through in-vitro analysis for their significance as biomarkers for cervical cancer.

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ISSN Online: 3007-3154
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Vol. 3 No. 8 (August) (2025)

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Vol. 3 No. 8 (August) (2025)

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ISSN Online: 3007-3154
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Vol. 3 No. 8 (August) (2025)

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