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Original Article

Association of TMPRSS2 Gene Polymorphism (rs12329760) with Prostate Cancer in Relation to Parental Consanguinity and Family History of Prostate Cancer

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Abstract

Background: Prostate cancer is a multifactorial disease with a strong genetic component. Variations in the TMPRSS2 gene, particularly the rs12329760 polymorphism, have been implicated in prostate carcinogenesis. In populations where consanguineous marriages are common, genetic susceptibility may be further amplified.

Objective: To determine the association of TMPRSS2 gene polymorphism (rs12329760) with prostate cancer and its relationship with parental consanguinity and family history of prostate cancer.

Methodology: A hospital-based case–control study was conducted involving 260 men aged over 50 years, including 130 histopathologically confirmed prostate cancer patients and 130 cancer-free controls. Genomic DNA was extracted from peripheral blood samples using the Chelex method. Genotyping of TMPRSS2 (rs12329760) was performed by Tetra-ARMS polymerase chain reaction. Genotype and allele frequencies were compared between cases and controls. Associations with parental consanguinity and family history of prostate cancer were evaluated using odds ratios (ORs) with 95% confidence intervals (CIs). Logistic regression analysis was applied to assess independent predictors, and Hardy–Weinberg equilibrium was tested in the control group.

Results: The CT and TT genotypes of TMPRSS2 (rs12329760) were significantly more frequent among prostate cancer patients compared with controls ($p < 0.001$). The T allele was also strongly associated with increased prostate cancer risk (OR: 3.76; 95% CI: 2.08–6.78; $p < 0.001$). A significant association was observed between the CT genotype and family history of prostate cancer (OR: 3.23; 95% CI: 1.17–8.90; $p = 0.03$). Similarly, the CT genotype showed a significant association with parental consanguinity (OR: 2.89; 95% CI: 1.09–7.60; $p = 0.03$).

Conclusion: TMPRSS2 gene polymorphism (rs12329760) is significantly associated with prostate cancer risk. The presence of parental consanguinity and a positive family history of prostate cancer further strengthens this association, highlighting the combined influence of genetic susceptibility and familial factors in prostate cancer pathogenesis.

Keywords: Family History of Prostate Cancer, Genetic Susceptibility, Parental Consanguinity, Prostate Cancer, TMPRSS2 Gene Polymorphism (rs12329760).

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy of the male genitourinary tract and remains a leading cause of cancer-related morbidity and mortality worldwide. The disease exhibits marked biological and clinical heterogeneity, ranging from indolent tumors with slow progression to highly aggressive, metastatic, and lethal forms despite appropriate treatment [1]. Among major cancers, prostate cancer demonstrates one of the highest heritability estimates, emphasizing the substantial contribution of genetic factors to disease susceptibility and progression [1].

The etiology of prostate cancer is multifactorial, involving a complex interplay between environmental exposures, lifestyle behaviors, hormonal influences, and inherited genetic variation [2]. Several modifiable risk factors including dietary patterns rich in animal fats and dairy products, obesity, smoking, physical inactivity, and alcohol consumption have been implicated in prostate carcinogenesis [3,4]. However, non-modifiable factors such as advancing age, ethnicity, circulating androgen levels, family history of prostate cancer, parental consanguinity, and genetic polymorphisms play a particularly critical role in determining individual risk [4].

Family history of prostate cancer is one of the strongest established risk factors for the disease. Epidemiological studies consistently demonstrate that men with an affected first-degree relative, such as a father or brother, have a two- to threefold increased risk of developing prostate cancer compared with those without a family history [5,6]. The risk is further amplified when multiple relatives are affected or when diagnosis occurs at a younger age [7]. These observations strongly support a hereditary component in prostate cancer pathogenesis and highlight the importance of identifying genetic variants that contribute to familial clustering.

At the molecular level, prostate cancer is characterized by a wide spectrum of genomic alterations, including single nucleotide polymorphisms (SNPs), point mutations, microsatellite instability, copy number variations, and chromosomal rearrangements [8]. These genetic alterations underlie the clinical heterogeneity of the disease and influence tumor initiation, progression, and therapeutic response. Among the genes implicated in prostate carcinogenesis, TMPRSS2 (transmembrane protease serine 2) has attracted considerable attention due to its androgen-regulated expression in prostate epithelial cells and its role in oncogenic gene fusions [9].

TMPRSS2 is a serine protease that is highly expressed in normal and malignant prostate tissue and is regulated by androgen receptor signaling [9]. One of the most well-characterized molecular events in prostate cancer is the fusion of TMPRSS2 with members of the ETS transcription factor family, particularly ERG. This fusion places the oncogenic ERG transcription factor under androgen control, leading to aberrant gene expression, enhanced tumor growth, and progression toward metastatic disease [8,9]. Beyond gene fusions, inherited polymorphisms within the TMPRSS2 gene may further modulate prostate cancer risk.

The TMPRSS2 rs12329760 polymorphism, a functional single nucleotide variant, has been associated with an increased risk of prostate cancer in several populations [8]. This polymorphism is thought to influence TMPRSS2 protein structure or function, potentially altering downstream signaling pathways involved in prostate tumorigenesis. However, the strength and nature of this association appear to vary across ethnic groups, underscoring the need for population-specific investigations.

In regions where consanguineous marriages are common, such as South Asia and the Middle East, the impact of inherited genetic variants may be further magnified due to increased homozygosity and transmission of risk alleles across generations. While parental consanguinity has been linked to several hereditary and multifactorial diseases, its relationship with prostate cancer particularly in conjunction with specific genetic polymorphisms remains poorly explored. To date, limited data are available examining the interaction between TMPRSS2 gene variants, parental consanguinity, and family history of prostate cancer.

Therefore, the present study was designed to investigate the association of TMPRSS2 gene polymorphism (rs12329760) with prostate cancer in a Pakistani population and to evaluate its relationship with parental consanguinity and family history of prostate cancer. Understanding these interactions may provide valuable insights into genetic susceptibility patterns, improve risk stratification in high-risk populations, and contribute to the development of targeted screening and preventive strategies.

Methodology

Study Design

This research employed a hospital-based case–control genetic association design to evaluate the relationship between TMPRSS2 gene polymorphism (rs12329760) and

prostate cancer, with particular emphasis on parental consanguinity and family history of prostate cancer. A dominant genetic model was assumed to assess genotype and allele-level associations between cases and controls.

Ethics

Ethical approval for the study was obtained from the Institutional Review Committee prior to commencement (Reference No. Riphah/IIMC/IRC/21/69). All procedures were conducted in accordance with the Declaration of Helsinki.

Written informed consent was obtained from all participants before enrollment, and confidentiality of clinical and genetic data was strictly maintained throughout the study period.

Setting

The study was conducted at the Department of Biochemistry, Islamic International Medical College (IIMC), Rawalpindi. Participant recruitment and sample collection were carried out at the Surgical Unit of Railway Hospital, Rawalpindi, and the Urology Department of the National Institute of Rehabilitative Medicine (NIRM), Islamabad.

Data collection spanned one year, from October 2021 to September 2022.

Table 1: Primer's Sequence.

Primer Name	5´ to 3´ Sequence
rs760-FI-C	CAGGACTTCCTCTGAGATGAGTAAAC
rs760-RI-T	GACCAAACTTCATCCTTCCGA
rs760-FO	AGGAGTCTATAGAGGCCAAGGAGGA
rs760-RO	GGTGAAACCCCATCTCTAATAAAACAG

Table 2: Temperature and duration of polymerase chain reaction (repeated for 35 cycles)

Steps	Stage	Temperature	Duration
Initial denaturation	I	95°C	3 minutes
Denaturation	I	95°C	30 seconds
Annealing	II	59°C	40 seconds
Extention	III	72°C	30 seconds
Final extention	III	72°C	5 minutes
Storage at 4°C for 30 minutes			

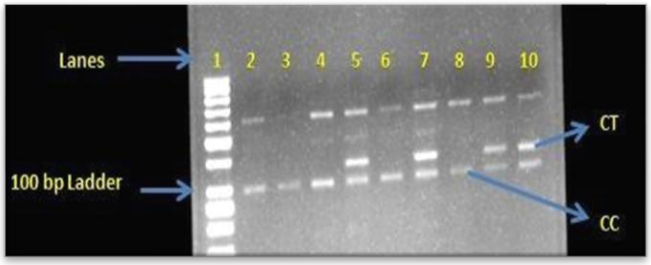


Figure 1: Electrophoretogram on 2% agarose gel showing amplified PCR products of *TMPRSS2* gene polymorphism (rs12329760) in controls with DNA marker of 100 bp, Lane represents 100 bp ladder, Lanes 2, 3, 4 ,6 & 8 represent CC-genotype, Lanes 5,7, 9 & 10 represent CT-genotype in cases

Study Size

Sample size estimation was performed using G*Power software for a case–control genetic association study under a dominant model. Assuming a minor allele frequency (MAF) of approximately 0.22, an expected odds ratio of 2.0, a two-sided alpha of 0.05, and 80% statistical power, a minimum of 130 participants per group was required, yielding a total study population of 260 [10].

Data Sources/Measurement

Venous blood samples (3 mL) were collected under aseptic conditions in EDTA vacutainers and stored at 4–8 °C until processing. Genomic DNA was extracted using the Chelex method. Genotyping of rs12329760 was performed using Tetra-ARMS polymerase chain reaction (PCR) with allele-specific primers designed via Primer3Plus software. PCR amplification was carried out in a Veriti™ 96-well thermal

cycler, followed by electrophoretic separation on 2% agarose gel stained with ethidium bromide. Genotypes were determined based on band patterns visualized under UV illumination [11-13].

Bias

To reduce selection bias, cases and controls were recruited from the same healthcare facilities and geographical region. Hardy–Weinberg equilibrium testing was applied to the control group to rule out genotyping errors and population stratification. Laboratory personnel performing genotyping were blinded to participants' clinical status to minimize observer bias.

Quantitative Variables

Genotype and allele frequencies were expressed as counts and percentages. Age was treated as a continuous quantitative variable, while parental consanguinity and family history of prostate cancer were analyzed as categorical variables.

Statistical Methods

Statistical analysis was performed using SPSS version 22 for Windows. Descriptive statistics were calculated for demographic and genetic variables. Associations between TMPRSS2 genotypes/alleles and prostate cancer were assessed using odds ratios (ORs) with 95% confidence intervals (CIs) derived from 2×2 contingency tables. Logistic regression analysis was applied to adjust for covariates including age, family history, and parental consanguinity. Hardy–Weinberg equilibrium was evaluated in the control group to confirm genotype distribution validity. A p-value < 0.05 was considered statistically significant

Results

Participants

A total of 260 male participants were included in the final analysis, comprising 130 prostate cancer patients (cases) and 130 cancer-free individuals (controls). All participants were aged above 50 years. Cases were histopathologically confirmed prostate cancer patients recruited from urology and surgical units, while controls were selected from the same hospitals and had no clinical or laboratory evidence of prostate malignancy. All enrolled participants provided complete demographic, clinical, and genetic data and were included in genotype and allele-based analyses.

Descriptive Data

Genotype distribution of the TMPRSS2 gene polymorphism (rs12329760) differed markedly between cases and controls. Among prostate cancer patients, 41% exhibited the CC genotype, 47% the CT genotype, and 12% the TT genotype. In contrast, controls predominantly carried the CC genotype (72%), followed by CT (25%) and TT (3%) genotypes. Allele frequency analysis revealed that the C allele was more frequent in controls (85%) than in cases (64%), whereas the T allele was substantially more prevalent among cases (35%) compared with controls (15%). The genotype distribution in the control group conformed to Hardy–Weinberg equilibrium ($\chi^2 = 1.42$, $p = 0.23$), supporting the reliability of genotyping and the absence of population stratification.

Outcome Data

A high proportion of prostate cancer patients reported parental consanguinity, with 96 cases (74%) affected, compared with 38 controls (28%). Similarly, family history of prostate cancer was reported in 95 cases (73%) and 34 controls (26%).

When stratified by genotype, parental consanguinity and family history were more frequently observed among individuals carrying the CT and TT genotypes, particularly in the case group. These patterns suggested a possible interaction between genetic susceptibility and familial risk factors in prostate cancer development.

Main Results

Statistical analysis demonstrated a strong and statistically significant association between TMPRSS2 (rs12329760) polymorphism and prostate cancer. Compared with the CC genotype, individuals carrying the CT genotype had a 3.30-fold increased risk of prostate cancer (OR: 3.30; 95% CI: 1.77–6.12; $p < 0.001$), while those with the TT genotype showed an even higher risk (OR: 7.02; 95% CI: 1.87–26.34; $p < 0.001$) (Table 03). At the allele level, the T allele was significantly associated with prostate cancer risk (OR: 3.76; 95% CI: 2.08–6.78; $p < 0.001$), whereas the C allele showed no statistically significant protective association. Further analysis revealed that the CT genotype was significantly associated with parental consanguinity among cases (OR: 2.89; 95% CI: 1.09–7.60; $p = 0.03$) and with family history of prostate cancer (OR: 3.23; 95% CI: 1.17–8.90; $p = 0.03$) (Table 04). Associations involving the TT genotype showed similar trends but did not reach statistical significance, likely due to smaller subgroup sizes.Binary logistic regression analysis confirmed that age, family history of prostate cancer, and parental consanguinity were independently associated with carriage of the T allele among prostate cancer patients. Increasing age emerged as a particularly strong predictor (adjusted OR: 210.20; $p < 0.001$), while both family history and cousin marriage significantly modified genetic risk (Table 05).

Table 3: Genotype and allele frequencies of cases and controls (n=260).

Genotype	Cases (N=130) N(%)	Controls (N=130) N(%)	Odds ratio (95% CI)	p-value
CC(reference)	53(41)	94(72)	1	---
CT	61(47)	33(25)	3.30(1.77-6.12)	< 0.001
TT	16(12)	4(3)	7.02(1.87-26.34)	< 0.001
Alleles				
C	167(64)	219(85)	1.59(0.98-2.57)	0.056
T	93(35)	41(15)	3.76(2.08-6.78)	< 0.001
Hardy-Weinberg equilibrium for controls group				
Group	**χ² value**	**p-value**	**Interpretation**	
Controls (n = 100)	1.42	0.23	In equilibrium	

CI: Confidence Interval, OD: Odds ratio, p-value <0.05–statistically significant

Table 4: Association of genotypes of TMPRSS2 (rs 12329760) in prostate cancer patients with parental consanguinity and family history of prostate cancer (n=260).

	Parental Consanguinity			
Genotypes	**Cases, (N=130) N(%)**	**Controls (N=130) N(%)**	**Odds Ratio (95%CI)**	**p-value**
Present	96(74)	38(28)		
CC	36(68.3)	24(25)	1	-----
CT	47(76.6)	11(33)	2.89(1.09-7.6)	0.03
TT	13(83.3)	3(75)	3.21(0.63-16.39)	0.18
	Family History of Prostate cancer			
Genotypes	**Cases, N=130 N(%)**	**Controls, N=130 N(%)**	**Odds Ratio (95%CI)**	**p-value**
Present	95(73)	34(26)		
CC	35(66)	22 (23.6)	1	-----
CT	47 (77)	9 (28.0)	3.23(1.17-8.90)	0.03
TT	13(83.3)	3 (66.7)	3.14(0.61-16.14)	0.18

Table 5: Association of T-allele of TMPRSS2 gene (rs 12329760) in prostate cancer patients with parental consanguinity and family history of prostate cancer (n=260).

Predictor Variable	B	S.E.	Wald	Df	p-value	Adjusted Odds Ratio (Exp B)	95% CI (approx.)
Age	5.348	0.575	86.6	1	< 0.001	210.20	(110 – 400)
Family history of prostate cancer	– 1.385	0.354	15.3	1	< 0.001	0.25	(0.12 – 0.52)
Parental consanguinity (cousin marriage)	– 1.215	0.340	12.8	1	< 0.001	0.30	(0.15 – 0.60)

Discussion

TMPRSS2 gene polymorphism (rs12329760) has been previously identified as a genetic risk factor for prostate cancer [14]. The present study was designed to further explore the association of this polymorphism with parental consanguinity and family history of prostate cancer, thereby providing insight into its potential role in the etiology and pathogenesis of prostate cancer. Our findings demonstrated a significant association between TMPRSS2 (rs12329760) and prostate cancer risk, which is consistent with the study conducted in an Indian population by Bhanushali et al., who also reported a strong association between this polymorphism and increased susceptibility to prostate cancer [15].

When stratified by familial risk factors, our results revealed significant associations between TMPRSS2 (rs12329760) and both family history of prostate cancer and parental consanguinity. Specifically, individuals carrying the CT genotype exhibited a significantly increased risk of prostate cancer in the presence of a positive family history (OR: 3.23; 95% CI: 1.17–8.90; $p < 0.03$). This finding is in agreement with a previous Colombian study by Tan et al., which also demonstrated a significant relationship between TMPRSS2 gene polymorphism and familial aggregation of prostate cancer [16].

The importance of family history as a major risk determinant for prostate cancer has been well established. Brook et al. reported that prostate cancer is among the malignancies with the highest heritability, underscoring the substantial contribution of inherited genetic factors to disease development [17]. Similarly, Ang et al. observed that individuals without a first- or second-degree family history of prostate cancer were more likely to present with low-grade disease at diagnosis, suggesting a protective effect in the absence of familial risk; however, these studies did not evaluate TMPRSS2 gene polymorphism [18]. Furthermore, Nathan J et al. highlighted family history as a significant predictor of prostate cancer diagnosis, even at low prostate-specific antigen levels, emphasizing the clinical relevance of inherited risk factors [9].

Importantly, our study identified a significant association between TMPRSS2 (rs12329760) polymorphism and parental consanguinity, with the CT genotype conferring an increased risk of prostate cancer (OR: 2.89; 95% CI: 1.09–7.60; $p = 0.03$). To the best of our knowledge, there are no prior studies evaluating the relationship between TMPRSS2 polymorphism and parental consanguinity in prostate cancer. Therefore, this study represents a novel contribution to the existing literature, highlighting the potential role of consanguineous marriages in amplifying inherited genetic risk for prostate cancer in susceptible populations.

Conclusion

This study provides strong evidence that the TMPRSS2 gene polymorphism (rs12329760) is significantly associated with prostate cancer risk. The association is further strengthened in individuals with parental consanguinity and a positive family history of prostate cancer, highlighting the combined impact of genetic susceptibility and familial factors. These findings suggest that TMPRSS2 (rs12329760) may serve as a potential genetic marker for prostate cancer risk assessment, particularly in populations with high rates of consanguineous marriages. Incorporation of genetic screening alongside family history assessment may improve early detection and risk stratification strategies.

Limitations of the Study

Despite its strengths, this study has certain limitations. The sample size, although adequately powered for primary genetic association analysis, may have limited the detection of statistically significant associations for less frequent genotypes, particularly the TT genotype. Additionally, modifiable lifestyle and environmental risk factors, such as diet, physical activity, smoking, and obesity; were not evaluated and may act as confounders in prostate cancer risk assessment. Future large-scale, multicenter studies incorporating gene–environment interactions and functional analyses of TMPRSS2 polymorphisms are warranted to further elucidate the mechanisms underlying prostate cancer susceptibility.

Authors' Contributions:

All authors meet the ICMJE criteria for authorship.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.

Author 6&7: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

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