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ACE2 and TMPRSS2 polymorphisms in various diseases with special reference to its impact on COVID-19 disease

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ABSTRACT

Background: A carboxypeptidase protein called ACE2 is found in many organs. ACE2 protein can play a pivotal role to regulate the pathological changes of several diseases including COVID-19. *TMPRSS2* gene is expressed in many human tissues and plays a critical role in spreading the infection of the viruses including coronavirus and progression of prostate cancer, and hence could be used as a potential drug target. There are limited reports on occurrence of genetic polymorphism of *ACE2* and *TMPRSS2* in general population, expressions in pathological conditions, and its impact on COVID-19 disease. Hence we comprehended the occurrence of *ACE2, TMPRSS2* polymorphism in general population, expression in various diseases and its impact on COVID-19 disease.
Method: We utilized multiple databases, PubMed (Medline), EMBASE and Google Scholar for literature search.
Description: ACE2 polymorphisms have significant linkages with various diseases, including severity of SARS-CoV-2 infection. Genetic variations of these genes contribute to individual's genetic susceptibility to viral infection and its subsequent clearance. The diversity and variations in the population distribution of these genes, might greatly influence and in turn reflect into the observed population and gender differences of the severity and clinical outcomes of SARS-CoV-2 infection.
Conclusion: There are diversities in distribution of *ACE2* and *TMPRSS2* polymorphisms among different populations. Analyzing the genetic variants and expression of *ACE2* and *TMPRSS2* genes, in a population may provide the genetic marker for susceptibility or resistance against the coronavirus infection, which might be useful for identifying the susceptible population groups for targeted interventions and for making relevant public health policy decisions.

1. Introduction

ACE2 is a negative controller of Renin Angiotensin system (RAS) in the human body. Angiotensin converting enzyme 2 (ACE2) causes conversion of Angiotensin (Ang) I to Ang (1–9) and degrades Ang II into Ang (1–7). Ang II acts in pro-inflammation, pro-fibrosis, vasoconstriction whereas Ang (1–7) is vasodilator peptide, anti-proliferative and apoptotic [1]. ACE2 protein is present in mucosa of oral and nasal passages, nasopharynx, lungs, skin, lymphatic system, liver, stomach, small intestine, colon, kidney, brain, heart, vascular endothelial, and smooth muscle cells [2]. ACE2 regulates the patho-physiological changes of important organs such as the lungs, kidneys, heart and gut [3]. It is associated with the progression of tissue injury, chronic diseases and serves as receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4].

ACE2, occupies 39.98 kb of genomic DNA, with 20 introns and 18 exons, is situated on chromosome Xp22 [5]. It is type I membrane-bounded glycoprotein which contains a catalytic domain made up of 805 amino acids [6]. The functional domains of the gene contain N-terminal signal peptide region, AC-terminal transmembrane anchoring region, and an HEXXH zinc-binding metalloprotease motif [7]. Single nucleotide polymorphisms (SNPs) in *ACE2* may result in modulation of RAS pathway and associated cardiovascular diseases [8]. *ACE2* rs4240157, rs4646155, and rs4830542 polymorphisms are related with hypertension (HT) [9–13]. Also rs2074192, rs233575, and rs2158083 polymorphisms has association with pathological variations

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of HT in Teens Canadian cohort [14]. *ACE2* rs21068809 C/T polymorphism was found to be related to occurrence and clinical manifestations of HT in Indian population [15,16]. *ACE2* 8790 G/A polymorphism was an indicator of susceptibility to HT in Brazilian cohorts [17].

ACE I/D polymorphism was linked with the diabetes, cancer, heart failure and hypertension [18] which are the comorbidities and risk factors for severe COVID 19 disease. The D allele of *ACE* I/D polymorphism could be important for SARS-CoV-2 disease progression which is subject of further research. High degree of genetic polymorphism involving *ACE*2 gene, might be responsible for population wise differences and variable susceptibilities for different disease conditions among population. Hence study of *ACE2* polymorphism in general populations might be important for understanding the susceptibility or resistance to either viral infection or others disease conditions.

TMPRSS2 mRNA is expressed in many tissues such as prostate, breast, bile duct, kidney, colon, small intestine, pancreas, ovary, salivary gland, stomach, and lung [19,20]. TMPRSS2 protein is expressed in aerodigestive tract.

A cell surface protein coding gene, transmembrane protease serine 2 (*TMPRSS2*) gene is associated with spread of influenza, corona viruses and development of prostate cancer [21–28]. *TMPRSS2* gene plays an important role in initial phase of the SARS-CoV-2 infection, thus targeting the expression or activity of *TMPRSS2* could be a potential candidate for anti- COVID-19 interventions [28].

TMPRSS2 is located on chromosome 21q22.321 [29] ~44 kb in length and contain 14 exons. A 15-bp androgen response element is present at position −148 relative to the putative transcription start site [30]. Camostat mesylate (Serine protease inhibitor) is utilized to block the TMPRSS2 activity [22–26]. In a genomic region of expression of quantitative trait locus (eQTL) variants includes *TMPRSS2* and *MX1* gene. *MX1* gene encodes a guanosine triphosphate (GTP)-metabolizing protein, which influences the cellular antiviral defense. The eQTL variant rs35074065 is linked with the overexpression of *TMPRSS2* and under expression of *MX1* splicing isoform [31,32]. This may give rise to enhanced susceptibility to viral infection or impaired cellular antiviral response.

Till date, comprehensive report on occurrence of *ACE2* and *TMPRSS2* polymorphisms in general population, expressions in various diseases has not been published. Hence we are presenting here a comprehensive review on occurrence of *ACE2, TMPRSS2* polymorphism in general population, expression in various diseases and its impact on acquisition, progression and severity of COVID-19 disease.

2. ACE2, TMPRSS2 and COVID-19 disease

The incidence and severity of COVID-19 disease varies worldwide [31]. Initially, SARS-CoV-2 infection occurred in Asian countries, followed by Southern European countries, which experienced much higher morbidity and mortality rates [33,34]. SARS-CoV-2 infection transmission occurs mainly through respiratory droplets and direct contact with the virus [35]. The pathogenesis of SARS-CoV-2 infection might be influenced by host genetic factors *ACE2* and Ang-II receptor type 2 gene, both are situated on the X-chromosome, *TMPRSS2*, pre-existing comorbidities, nonmodifiable factors like age and sex together. Thus many factors collectively determine the fate and prognosis of SARS-CoV-2 infection, also affecting the associated mortality. Basically, X-linked heterozygous alleles could act in favor of females by imparting a greater sexual dimorphism which might counteract viral infection, inhibiting local inflammation and thus protecting female from severe adverse outcomes of COVID-19.

The incidence and progression of COVID-19 disease depends on the interaction between the virus-host. Multiple factors from host like genetic polymorphisms, gender, age, life style status and nutritional, physical status, neuroendocrine-immune regulation and ethnicity contribute while factors such as type of virus, mutations present within the virus, viral titer, viral load, and viability of the virus act as viral factor. COVID-19 disease showed a variation in symptoms, from mild or asymptomatic, influenza-like symptoms, severe pneumonia, acute respiratory distress and even death. Also a wide difference was observed in outcome of Novel Coronavirus (2019-nCoV) infection between males and females. This variation is expected to be multifactorial including genetics.

Three strains of coronavirus, SARS-CoV-2, SARS-CoV and NL63 utilize the ACE2 receptor, a zinc metalloprotease. Evidence suggested that variations in host *ACE2* sequences and viral spike protein both may affect the trans-species spread of viral infection [36–40].

The transmembrane spike (S) glycoprotein of virus binds to the ACE2 making it essential for the invasion of the virus into the host cell, followed by attachment of the virus to the target cells. S- protein priming by TMPRSS2, therefore necessary for the correct maturation of these proteins that enter the cell through ACE2, allowing the bonding of viral and cellular membranes, resulting in virus entry and replication in the host cells [23–37]. As binding of SARS-CoV-2 with ACE2 is a prerequisite for the entry in the host cells, hence the distribution and expression of *ACE2* in target organ could be important determinant for the initiation of virus infection and its progression.

Spike (S) proteins of virus gets recognized by the critical lysine 31 present on the ACE2 receptor. The residue 394 (glutamine) in the SARS-CoV-2 receptor-binding domain (RBD) binds with ACE2 receptor. Followed by TMPRSS2 facilitated adhesion of the virus with host cell membrane, thus allowing the virus entry into host cell cytosol and subsequent virus replication [4,41].

ACE I/D genotype occurs in different populations, which might impact the incidence of the SARS-CoV-2 infection. In European population, the deletion genotype DD of *ACE1* was associated with SARS-CoV-2 infection [42,43]. In Europe and Southern Europe, the occurrence of D allele of *ACE1* was higher as compared to Asian population [43]. This might be one of the reasons behind the higher incidences of morbidity and case fatality in Europeans as compared to Asians. However, frequency of D allele is low in India as compared to East Asian Chinese and Korean populations [44]. Higher frequency of I allele, as reported by the studies in different Indian population subgroups could be an explanation behind the lower incidence of SARSCoV-2 infection in Indian population [45–49]. Report from China suggested that Asians neither have distinctive *ACE2* genetic polymorphisms nor high level expressions of ACE2 [50]. On the contrary, another study has denied any relationship between the human *ACE2* variants and susceptibility to SARSCoV-2 infection [51]. Genetic variants of A*CE2* gene affect the interaction between host receptor and viral spike protein [52]. Significant variations in the levels of *ACE2* expression in lung tissues of transcontinental human populations are reported but still the evidence is non-conclusive [33,34]. Hence looking for the abundance of *ACE2* gene among different populations will be important. This could be one of the important area for research of genetic epidemiology, with an objective to explore the reason for differential spread and mortality of COVID-19 disease in different regions of the world.

TMPRSS2 expression is crucial for spread of virus and pathogenesis. Genetic variation in this gene may modulate genetic predisposition to infection and virus clearance in the host. As *TMPRSS2* is expressed significantly more in androgen sensitive tissues like prostate and testis, male gender seems to be more vulnerable for acquisition of infection. This may be the cause of gender specific differential infection rates [31].

eQTLs is found in high number for *TMPRSS2* of allele frequency of whom varies among the different populations. In East Asians, the *TMPRSS2* allele is found in lower frequency [31] Gender differences in case fatality and morbidity could also be explained by the presence of TMPRSS2: ERG fusion protein in men specific diseases like prostate cancer and the effective regulation of *TMPRSS2* by androgens. The expression of *TMPRSS2* mRNA level in lung tissue of men is not different than that of women. However, there was a broad range variation in expression of mRNA levels among both genders [28]. In women,

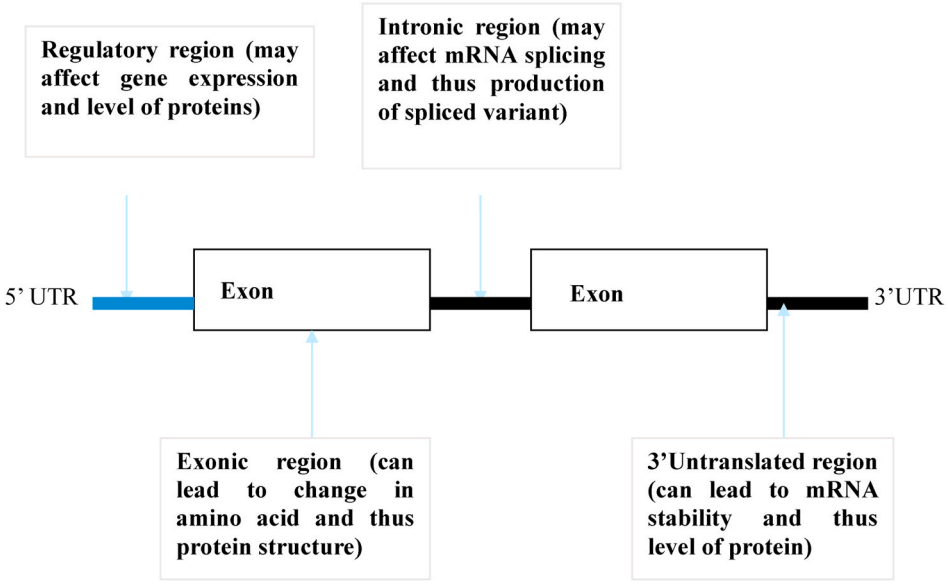

Fig. 1. Role of polymorphism.

androgens are expressed at low levels which in turn could affect *TMPRSS2* expression [53,54]. Therapies for androgen receptor-inhibition might decrease the vulnerability to severe COVID-19 disease through modulation of *TMPRSS2* expression, thereby in turn reducing the mortality. Differential distribution of Lung-specific *TMPRSS2* may display different profiles of susceptibility or resistance of virus. In the lung of men, *TMPRSS2* expression might be higher that could improve the viral ability to enter host cells by enhancing membrane adhesions [31].

TMPRSS2 is known as an androgen responsive gene [55]. *TMPRSS2* rs2070788, rs7364083, rs9974589 polymorphism have a significant role in general. *TMPRSS2* rs8134378 polymorphism increase the *TMPRSS2* expression in males which favor virus membrane fusion [56,57] in similar types of viruses, namely A (H1N1) and A (H7N9) influenza [58]. In postmenopausal female, the production of estrogen become reduced, which affects the expression of *TMPRSS2*. The common polymorphisms of *ACE1* and *ACE2* genes act to enhance their mutual expression levels. This might cause fibrosis, hyper coagulation, apoptosis and increased capillary permeability in the pneumocytes, promoting lung injury and lung failure after SARS-CoV-2 infection.

The host cell protease furin is a type I transmembrane protein which cleaves the SARS-CoV-2 spike protein at the S1/S2 site and play a role in spike-driven viral entry into lung cells. Since furin is highly expressed in the lungs, an enveloped virus that infects the respiratory tract may successfully exploit this convertase to activate its surface glycoprotein. Examination of genetic variation of Furin gene will provide information about furin cleavage sequence (PRRARS|V) which can be used as a target in infected individuals.

3. ACE2 polymorphism in general population

In the population, genetic polymorphism in 5′ untranslated region genes may affect gene expression and levels of proteins in the individuals. Genetic variants of exonic region genes can lead to change in amino acid and thus protein structure of the individuals. Genetic variations in intronic region gene may affect mRNA splicing and thus production of spliced variant of individuals. Polymorphism in 3' untranslated region gene can lead to mRNA stability and thus level of protein in the individuals. Genetic polymorphism in coding region protein can affect amino acid substitution, altered splice variant and protein truncation while as polymorphism in larger segment stop the normal function of gene because of deletion of the gene. If there is duplication of gene which increase the activity because of gain of function (Fig. 1).

Inter-individual and inter-population variations in the clinical outcomes of COVID-19 disease, following the exposure of SARS-CoV-2 infection or virus are linked with genetic background variability. Difference in pathophysiological responses of individuals to the infection and diseases condition may get influenced by genetic variants of ACE genes, their different levels of expression and functions.

ACE2 I/D polymorphism greatly varies from population to population [59]. SNPs rs200180615 and rs140473595 found in Han Chinese population with the allele frequency, AF < 0.01. Polymorphism rs2285666 occurred at higher AF in South Han Chinese populations

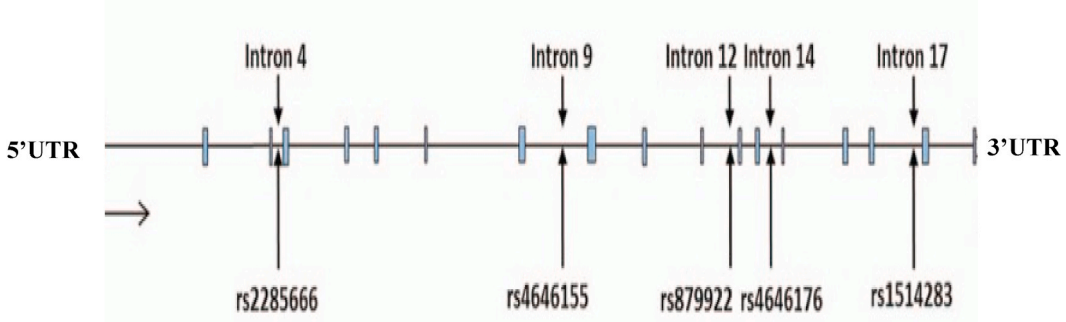

Fig. 2. ACE2 polymorphism (Adopted from Zhang et al., 2018).

Table 1
Genetic polymorphism of ACE2 and TMPRSS2 in general population.

S.No	Gene & Choromo somal location	rs number of SNPs	Genotypes	Genotype Frequency in Healthy controls	Population	Reference
1	*ACE2* (Xp22.2)	rs1514283 T/C	TT	920(96.2)	China	Zhang et al., 2018
			CT	30(3.1)		
			CC	6(0.7)		
2	*ACE2* (Xp22.2)	rs4646155 C/T	CC	920(96.2)	China	Zhang et al., 2018
			CT	30(3.1)		
			TT	6(0.7)		
3	*ACE2* (Xp22.2)	rs4646176 C/G	CC	916(96.2)	China	Zhang et al., 2018
			CG	30(3.2)		
			GG	6(0.6)		
4	*ACE2* (Xp22.2)	rs879922 G/C	GG	908(95.2)	China	Zhang et al., 2018
			CG	40(4.2)		
			CC	06(0.6)		
5	*ACE2* (Xp22.2)	rs1514283 T/C	TT	920(96.2)	China	Zhang et al., 2018
			CT	30(3.1)		
			CC	6(0.7)		
6	ACE2 (Xp22.2)	rs4646155 C/T	CC	920(96.2)	China	Zhang et al., 2018
			CT	30(3.1)		
			TT	6(0.7)		
7	*ACE2* (Xp22.2)	rs4646176 C/G	CC	916(96.2)	China	Zhang et al., 2018
			CG	30(3.2)		
			GG	6(0.6)		
8	*ACE2* (Xp22.2)	rs2074192 C/T	CC	118(50.6)	China	Yi Luo et al., 2019
			TC + CC	115(49.4)		
9	*ACE2* (Xp22.2)	rs2106809 C/T	CC + CT	121(51.9)	China	Yi Luo et al., 2019
			TT	12(48.1)		
10	*ACE2* (Xp22.2)	rs4240157 C/T	CC + CT	43(18.5)	China	Yi Luo et al., 2019
			TT	190(81.5)		
11	*ACE2* (Xp22.2)	rs4646155 C/T	CC	211(90.6)	China	Yi Luo et al., 2019
			TT + CT	22(9.4)		
12	*ACE2* (Xp22.2)	rs4646188 C/T	CC	74(31.8)	China	Yi Luo et al., 2019
			TT + CT	159(68.2)		
13	*ACE2* (Xp22.2)	rs4830542 C/T	CC + CT	43(18.5)	China	Yi Luo et al., 2019
			TT	190(81.5)		
14	*ACE2* (Xp22.2)	rs879922 C/G	CC + CG	40(17.2)	China	Yi Luo et al., 2019
			GG	193(82.8)		
15	*ACE2* (Xp22.2)	rs2106809 I/D (C > T)	CC		India	Patnaik et al., 2014
			CT			
			TT			
16	*ACE2* (Xp22.2)	rs1800764-3903C/T	TT	50(30)	Poland	G. Deja et al., 20140
			CT	84(49)		
			CC	36(21)		
17	ACE2 (Xp22.2)	rs4459609-5486A/C	AA	60(35)	Poland	G. Deja et al., 20140
			AC	83(48)		
			CC	30(17)		
18	*ACE2* (Xp22.2	rs2746071-638A/G	AA	102(59)	Poland	G. Deja et al., 20140
			AG	58(34)		
			GG	13(8)		
19	*ACE2* (Xp22.2	rs2106809 I/D	II	34(23.77)	Saudi Arabia	Jamal SM Sabir et al., 2019
			ID	32(22.37)		
			DD	77(53.84)		
20	*TMPRSS2* (21q22.3)	rs2070788 G/A	GG	9 (8.5)	Hong Kong	Zhongshan Cheng et al., 2015)
			GA	43 (40.6)		
			AA	54 (50.9)		
21	*TMPRSS2* (21q22.3)	rs383510 T/C	TT	7 (6.6)	Hong Kong	Zhongshan Cheng et al., 2015)
			TC	47 (44.3)		
			CC	52 (49.1)		

compared to Mixed American, African, and European populations [51]. The reported frequency of homozygous genotype was almost double in males (0.550), than that of females (0.310) in the Chinese population. The truncation variant Gln300ser of ACE2 was reported from China. Also, out of 32 variants studied, seven were linked to the active hotspots of infection in diverse populations [51].

Occurrence of *ACE2* rs1514283 T/C, rs4646155 C/T, rs4646176 C/G, rs879922 G/C, rs2074192 C/T, rs2106809 C/T, rs4240157 C/T, rs4646155 C/T, rs4646188 C/T, rs4830542 C/T, rs879922 C/G polymorphisms were reported in healthy population of China [60]. Incidence of *ACE2* rs2106809 I/D polymorphism was reported in healthy individuals of India and Saudi Arabia [61,62]. Genotype frequency of *ACE2* rs1800764-3903C/T, rs4459609-5486A/C, rs4459609-3678Ins/Del, and rs274601-638A/G polymorphisms were reported in general population of Poland [63] (Fig. 2, Table 1).

4. ACE2 expression and pathological conditions

ACE2 gene is expressed in the central nervous system, lungs and testis however, *ACE2* predominantly gets expressed in the cardiac, kidney, gastrointestinal tissues and alveolar epithelial cells [64,65]. Since ACE2 is more expressed in the alveolar epithelial cells (2), lungs could be explained as a primary target of SARS-CoV-2 infection [66] and knocking-out *ACE2* in mice suppressed SARS-CoV infection in the lung [67]. Correlation of *ACE2* expression with the susceptibility to SARS-CoV infection among cells is documented [68,69]. Overexpressing *ACE2* in vitro enhanced efficiently the replication of SARS-CoV, whereas neutralization by ACE2 antibodies inhibited replication of the virus in a

Table 2
Expression of *ACE2* and *TMPRSS2* genes in various organs and tissues.

S. No	Gene & chromosomal location	Expression in Human organs and tissues	Reference
1	*ACE2*(Xp22.2)	cardiovascular, renal and gastrointestinal tissues	(Mary Donoghue et al., 2000).
2	*ACE2*(Xp22.2)	brain lung and testis	(Harmer et al., 2002).
3	*ACE2*(Xp22.2)	alveolar epithelial cells	(Hamming et al., 2004),
4	*ACE2*(Xp22.2)	cell lines	(Li et al., 2003).
5	*ACE2*(Xp22.2)	overexpression of *ACE2* ameliorates the impaired glucose homeostasis by reducing fastingblood glucose and improvement of glucose tolerance in diabetics	(Bindom et al., 2020).
6	*ACE2*(Xp22.2)	Over-expression of ACE1 receptor as in the presence of the ACE1 DD-genotype (i.e., rs4646994, rs1799752, rs4340, rs13447447) in combination with ACE2 downregulation due to SARS-CoV-2 infection and/or the presence of the ACE2 8790 G-allele (i.e., rs2285666), results in ACE1/ACE2 imbalance, leading to 'Renin Angiotensin System' over-activation (Ang-II) and ultimate lung failure.	(Donato Gemmati et al., 2020)
7	*TMPRSS2* (21q22.3)	Expressed in type 1 and 2 alveolar cells	(Waradon et al., 2003).
8	*TMPRSS2* (21q22.3)	mRNA expression is elevated in androgen-stimulated prostate malignant (LNCaP) cells	(Lin et al., 1999).
9	*TMPRSS2* (21q22.3)	expressions are correlated with initiation of SARS-CoV-2 and other viral infections of respiratory tract	(Stopsack et al., 2020)
10	*TMPRSS2* (21q22.3)	High expression of *TMPRSS2* is associated either with increased susceptibility to viral infection or to diminishedcellular immuneresponse against virus.	(Linda Kachuri et al., 2020).

dose-dependent manner [4].

Overexpression of *ACE2* acts as a corrective balancing mechanism for hyperglycemia induced activation of renin angiotensin aldosterone system. In diabetic mice, overexpression of *ACE2* stabilizes the impaired glucose homeostasis by reducing blood glucose level and improving glucose tolerance. Thus, *ACE2* could be used as a potential target, useful for maintenance of β-cell function in type 2 diabetes mellitus [70] (Table-2).

ACE2 is expressed in endothelial cells and various compartment of brain such as neurons, glial cells, astrocytes, and oligodendrocytes. The S1 protein of SARS-CoV-2 binds and attach with ACE2 receptor of endothelial cells may participate in the neurovascular damage of COVID-19 patients. Hence the brain tissue COVID-19 patients showed hyperemic and edematous and some degenerated neurons and raises the possibility that SARS-CoV-2 has the potential to infect neurons and glial cells throughout the CNS.

5. TMPRSS2 polymorphism in general population

The mammals have a highly conserved TMPRSS2 with amino acid Met160Val. TMPRSS2 rs12329760 polymorphism is present in the exonic splicing enhancer srp40 site, and variant allele of rs12329760 polymorphism could increase the chance of faulty expression due to potential disruption of the exonic splicing enhancer site. TMPRSS2 rs12329760 C/T polymorphism was associated with TMPRSS2-ERG fusion [71].

Patients with *TMPRSS2* rs2070788 and rs383510 polymorphisms were reported to have higher levels of *TMPRSS2* expression and are highly predisposed for viral infection with A(H7N9) in two different cohorts of influenza patients [31]. In East Asian population, the eQTL variants showed much lower allele frequencies (AFs) compared to high AFs in European populations, this is associated with higher pulmonary *TMPRSS2* expression [31].

The occurrence of deleterious variant was higher in Italians as compared to Europeans and East Asian population suggesting that Italians might have greater TMPRSS2 protein/activity, which may increase risk for severe course of disease [56]. However, older age along with deleterious variant could be one factor for disease lethality in Italians [56]. The missense substitution inVal160Met affects a residue away from the serine protease catalytic triad. The genomic rearrangements of *TMPRSS2* was found to be associated this variation, increasing the risk of prostate malignancy [72]. Occurrence of *TMPRSS2* rs2070788 G/A and rs383510 T/C polymorphisms were reported in healthy individuals of Hong Kong (Fig. 3, Table 1) [58].

6. TMPRSS2 expression and pathological condition

In Type 1 Type 2 alveolar cells and androgen-stimulated prostate cancer cells expression of *TMPRSS2* mRNA is elevated [73,74]. Androgen binds with androgen receptor and transduce a signal to mediate the upregulation of *TMPRSS2* mRNA [75]. Androgen treatment increases the *TMPRSS2* zymogen activation which might contribute in initiation and progression of prostate cancer, in an androgen-dependent way. *TMPRSS2* rs35074065 polymorphism is linked with the increased expression of *TMPRSS2* and decreased expression of *MX1* splicing isoform (Table- 2) [31]. Thus play a role in antiviral immune response.

7. Importance

Population studies on natural genetic variants and expressions of human *ACE2* and *TMPRSS2* genes, which influence the susceptibility to or resistance against the coronavirus infection has been very limited. Hence analyzing the genetic variants and expression of human *ACE2* and *TMPRSS2* gene may provide the genetic marker for susceptibility or resistance against the coronavirus infection. *ACE2* and *TMPRSS2* play a crucial role in initiation of SARS-CoV-2 infection, progression and prognosis of COVID-19 disease. The cross-transmission of the virus is

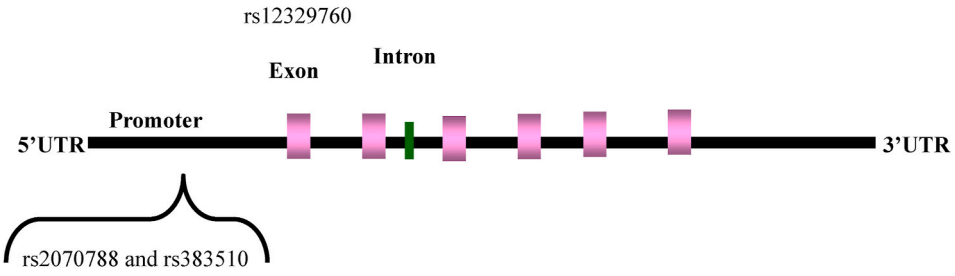

Fig. 3. *TMPRSS2* Gene polymorphism.

supported by the genetic variations in the coronavirus spike protein and host *ACE2* receptor gene. Hence knowing the polymorphism of *ACE2* and *TMPRSS2* genes would be helpful to forecast the progression and clinical outcomes of COVID-19 disease.

TMPRSS2 rs35074065 polymorphism is related to the over-expression of *TMPRSS2* and underexpression of MX1 splicing isoform, hence analyzing the *TMPRSS2* rs35074065 polymorphism among SARS-CoV-2 infected populations could predict the genetic susceptibility for either viral infection or for an impaired cellular antiviral response. The resistant variants of *TMPRSS2* to SARS-CoV-2 S-protein priming in varied populations has not been described. Hence analyzing the genetic variation in *TMPRSS2* gene among SARS-CoV-2 infected populations may provide the resistant variants to spike protein priming. Likewise, TMPRSS2 protein expression in respiratory tract of various populations has not been well addressed. Analyzing the TMPRSS2 protein expression in lung would be helpful to understand the differential susceptibility to coronavirus infections.

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Data availability statement

Data will be available on request by email.

Authors contribution

HariOm Singh: Overall supervision.
Ranjana Choudhari: Manuscript writing.
Vijay Nema: Manuscript Review & Revision.
Abdul Arif Khan: Manuscript Review.

Ethical approval

Not required.

Declaration of competing interest

No.

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