Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Lung Cancer 152 (2021) 199–201

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Evaluation of variant frequency in SARS-CoV-2 infection-related genes utilizing lung cancer genomic database

The numbers of cases of and deaths from COVID-19 in East Asian countries are obviously lower than those in other parts of the world (677.9 cases and 12.6 deaths per 1 million population in Japan, 4521 cases and 133.2 deaths per 1 million population in the world) [1]. Basic research has shown that angiotensin-converting enzyme 2 (*ACE2*) and transmembrane serine protease 2 (*TMPRSS2*) are crucial for SARS-CoV-2 infection. Recent studies have indicated that the genetic diversity of *ACE2* and *TMPRSS2* variants across races might affect these functions and the susceptibility, symptoms and outcome of SARS-CoV-2 infection [2–5]. Therefore, understanding racial differences in *ACE2* and *TMPRSS2* gene variants underlying the potential severity of COVID-19 is important.

We analyzed the coding variants of *ACE2* and *TMPRSS2* and their allele frequencies (AFs) in 350 Japanese patients with advanced-stage lung cancer using whole-exome sequencing data in a study that was part of the International Lung Cancer Genome Screening Project in East Asia (LC-SCRUM-Asia). In addition, we compared the observed genetic variants and their AFs with those of other Japanese cohorts and other ethnic populations using publicly available genomic databases: dbSNP, GnomAD and TOPMed.

In our Japanese lung cancer cohort, 9 and 7 variants were found in *ACE2* and *TMPRSS2*, respectively (Table 1). All the variants except for two intron variants near exons were missense changes. Silent amino acid changes were excluded from the analysis. The AFs of c. 439 + 4G > A in *ACE2* (rs2285666) and c.589 G > A in *TMPRSS2* (rs12329760) were much higher in East Asians (0.5281 and 0.4172, respectively) in both our cohort and another Japanese cohort (The Tohoku Medical Megabank Project database) than in Caucasians (0.3692 and 0.1722, respectively). On the other hand, c.23 G > T in *TMPRSS2* (rs75603675) was more frequent in Caucasians than in East Asians (0.2845 vs. 0.0141, respectively). The AFs of other variants were similar among the compared populations. The above-mentioned variants with significant AF differences might be associated with the differences in disease severity of COVID-19 between East Asians and Caucasians.

As far as we know, the biological significance of these variants in SARS-CoV-2 infection and clinical data for members of these cohorts with COVID-19 are unknown. Although further studies are needed to evaluate this matter, the present data may support our understanding of racial differences in COVID-19 severity and may help to overcome this pandemic.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

This work was supported by Japan Agency for Medical Research and Development, AstraZeneca, Bristol-Myers Squibb, Chugai, and Ono.

The sponsors had no control over the interpretation, writing, or publication of this work.

The first author, Yuji Shibata, received honorarium from Pfizer Inc., Bristol-Myers Squibb K.K., AstraZeneca K.K. and Taiho Pharmaceutical Co., Ltd., and research grant from Pfizer Inc., AstraZeneca K.K. and Ono Pharmaceutical Co., Ltd.

Co-responding author, Shingo Matsumoto, received honorarium from Novartis Pharma K.K. and research grant from Pfizer Inc., AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., MSD K.K., Eli Lilly Japan K.K. and Merck Biopharma.

Kiyotaka Yoh received research grant from Eli Lilly, Novartis, MSD, Taiho, Daiichi Sankyo, Bayer, Pfizer and Takeda and received honorarium from Boehringer Ingelheim and Kyowa Kirin.

Research grant which Koich Goto received is written below.

From Bristol-Myers Squibb K.K., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Amgen Astellas BioPharma K.K., Amgen Inc., Astellas Pharma Inc., AstraZeneca K.K., Boehringer Ingelheim Japan, Inc., DAIICHI SANKYO Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Ignyta, Inc., Janssen Pharmaceutical K.K., Kyowa Hakko Kirin Co., Ltd., Loxo Oncology, Inc., MEDICAL & BIOLOGICAL LABORATORIES CO., LTD., Merck Biopharma Co., Ltd., Merck Serono Co., Ltd., MSD K.K., Nippon Kayaku Co., Ltd., Novartis Pharma K.K., Pfizer Inc., Sumitomo Dainippon Pharma Co., Ltd., Sysmex Corporation., Taiho Pharmaceutical Co., Ltd., Thermo Fisher Scientific K.K., Xcoo, Inc. and Takeda Pharmaceutical Co., Ltd.

Honorarium which Koich Goto received is written below.

From Bristol-Myers Squibb K.K., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Amgen Astellas BioPharma K.K., AstraZeneca K.K., Boehringer Ingelheim Japan, Inc., Eli Lilly Japan K.K., Guardant Health Inc., Janssen Pharmaceutical K.K., Merck Biopharma Co., Ltd., MSD K.K., Nippon Kayaku Co., Ltd., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., Taiho Pharmaceutical Co., Ltd., Thermo Fisher Scientific K.K., and Takeda Pharmaceutical Co., Ltd.

Acknowledgements

This work was supported by Japan Agency for Medical Research and Development, AstraZeneca, Bristol-Myers Squibb, Chugai, and Ono.

References

[1] WHO reports, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

https://doi.org/10.1016/j.lungcan.2020.12.016
Received 29 November 2020
Available online 24 December 2020

Table 1
Coding variants of *ACE2* and *TMPRSS2* in Japanese lung cancer patients and racial comparisons of AFs.

Gene	Position	dbSNP rs#	Amino acid change	CDS	Japanese lung cancer patients (LC-SCRUM-Asia)						Genome database (freq.)								
					Zygosity				Total (N = 350)		ToMMo (JPN)	GnomAD						TOPMed	ExAC
					Hetero		Homo												
					N	freq.	N	freq.	N	freq.		AFR	AMR	ASJ	EAS	NFE	Whole		
ACE2	chrX: 15618865	-	p.E57G	c.170A > G	1	0.0029	-	-	1	0.0029	-	-	-	-	-	-	-	-	-
	chrX: 15610348	rs2285666	Intron Variant	c.439 + 4G > A	51	0.1457	152	0.4343	203	0.5800	0.4973	0.2204	0.3692	0.2590	0.5281	0.1991	0.2324	0.2503	0.1770
	chrX: 15609946	-	p.Y158C	c.473A > G	1	0.0029	-	-	1	0.0029	-	-	-	-	-	-	-	-	-
	chrX: 15603621	-	p.V293F	c.877 G > T	1	0.0029	-	-	1	0.0029	-	-	-	-	-	-	-	-	-
	chrX: 15596236	-	p.S425A	c.1273 T > G	-	-	1	0.0029	1	0.0029	-	-	-	-	-	-	-	-	-
	chrX: 15593829	rs191860450	p.I468V	c.1402A > G	-	-	1	0.0029	1	0.0029	0.0035	0.0000	0.0000	0.0000	0.0112	0.0000	0.0006	0.0010	0.0007
	chrX: 15589926	rs774469453	splice region variant	c.1665-7delT	-	-	-	-	not detected		0.0159	0.0009	0.0211	0.0000	0.0010	0.0006	0.0014	0.0062	0.0050
	chrX: 15589842	-	p.V581A	c.1742 T > C	1	0.0029	-	-	1	0.0029	-	-	-	-	-	-	-	-	-
	chrX: 15582333	rs769062069	p.R708Q	c.2123 G > A	-	-	1	0.0029	1	0.0029	-	-	-	-	-	-	0.0000	-	0.0000
	chrX: 15582298	rs41303171	p.N720D	c.2158A > G	-	-	-	-	not detected		-	0.0032	0.0043	0.0155	0.0000	0.0247	0.0153	0.0140	0.0165
	chrX: 15582250	-	p.Q736K	c.2206C > A	1	0.0029	-	-	1	0.0029	-	-	-	-	-	-	-	-	-

Gene	Position	dbSNP rs#	Amino acid change	CDS	Japanese lung cancer patients (LC-SCRUM-Asia)						Genome database								
					Zygosity				Total (N = 350)		freq.								
					Hetero		Homo				ToMMo (JPN)	GnomAD						TOPMed	ExAC
					N	freq.	N	freq.	N	freq.		AFR	AMR	ASJ	EAS	NFE	Whole		
TMPRSS2	chr21:42879909	rs75603675	p.G8V	c.23 G > T	3	0.0086	-	-	3	0.0086	0.0031	0.3279	0.2845	0.3681	0.0141	0.4169	0.3642	0.3516	0.3575
	chr21:42866439	rs61735791	p.A65T	c.193 G > A	4	0.0114	-	-	4	0.0114	0.0073	0.0010	0.0007	0.0003	0.0003	0.0029	0.0017	0.0020	0.0016
	chr21:42866388	rs201679623	p.Y82D	c.244 T > G	2	0.0057	-	-	2	0.0057	0.0010	0.0000	0.0000	0.0000	0.0061	0.0000	0.0002	0.0006	0.0005
	chr21:42866384	rs1016773134	p.P83L	c.248C > T	1	0.0029	-	-	1	0.0029	-	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	-
	chr21:42866331	rs574582815	p.V101l	c.301 G > A	1	0.0029	-	-	1	0.0029	-	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001
	chr21:42852497	rs12329760	p.V197M	c.589 G > A	165	0.4714	49	0.1400	214	0.6114	0.3837	0.2884	0.1722	0.1007	0.4172	0.2474	0.2801	0.2470	0.2502
	chr21:42842591	rs61735794	p.G422G	c.1266 G > A	-	-	-	-	not detected		-	0.0057	0.0189	0.0196	0.0000	0.0305	0.0203	-	0.0206

Genetic variants are listed if they were detected in a whole-exome sequence or if the AF was more than 0.01 in at least one of the databases.
Position numbers indicate distance from 5′ end of the original exon 1.
ToMMo: The Tohoku Medical Megabank Project, GnomAD: The Genome Aggregation Database, TOPMed: Trans-Omics for Precision Medicine, ExAC: The Exome Aggregation Consortium.
JPN: Japanese, AFR: African-American/African, AMR: Latino, ASJ: Ashkenazi Jewish, EAS: East Asian, NFE: Non-Finnish European.
141 patients have no variant in *ACE2* and 127 patients have no vatiant in *TMPRSS2*. Two patients have two variants in *ACE2* and five patients have two variants in *TMPRSS2*.

[2] P. Zhou, X.L. Yang, X.G. Wang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270–273.
[3] M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280.
[4] W. Li, C. Zhang, J. Sui, et al., Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2, EMBO J. 24 (2005) 1634–1643.
[5] R. Asselta, E.M. Paraboschi, A. Mantovani, et al., ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy, Aging (Albany NY). 12 (11) (2020) 10087–10098.

Yuji Shibata, Shingo Matsumoto*, Kiyotaka Yoh, Koichi Goto
Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

* Corresponding author.
E-mail address: shmatsum@east.ncc.go.jp (S. Matsumoto).