Human Cell (2021) 34:1937–1940
https://doi.org/10.1007/s13577-021-00601-4

LETTER TO THE EDITOR

Association of rs11549465 (C1772T) variant of hypoxia-inducible factor-1α with Covid-19 susceptibility. A population-based epidemiological study

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Received: 19 July 2021 / Accepted: 19 August 2021 / Published online: 23 August 2021

To the Editor,

Hypoxia in COVID-19 is the predominant clinical manifestation requiring immediate ventilation support [1, 2], failure to which may have the detrimental consequence of death. Adaptation to hypoxia is mediated through signaling via hypoxia-inducible factor (HIF), all three isoforms of which differ with respect to structurally related oxygen regulated component of the heterodimer, the α subunit (HIF-1α, 2α and 3α). Of these, HIF-1α activity is reported to be high in acute or intermittent hypoxia which occur in COVID-19 [3], whereas chronic hypoxia stimulates HIF-2α release, with biological function of 3α is yet to be established [2]. However, it is still unclear whether HIF-1α signaling is beneficial against COVID-19 or is a prognostic indicator of severity and deaths [4, 5]. Since host genetic factors play a crucial role in COVID-19 outcomes and vary amongst populations, we performed a population-based association study to unravel whether HIF-1α functional variants influence worldwide heterogeneity in COVID-19 risk and deaths.

Human HIF1α gene located on chromosome 14 has several variants, of which two non-synonymous polymorphisms such as Pro582Ser [rs11549465 (C1772T)] and Ala588Thr [rs11549467 (G1790A)] are functionally important owing to their regulation of expression, stability and association with various diseases [6]. Worldwide population prevalence data of these variants in healthy controls were retrieved from relevant published papers through literature search on PubMed, Google scholars and from public-databases for genomic variants (such as ALFRED and 1000 Genomes Project). Studies with insufficient data and those deviating from Hardy Weinberg Equilibrium (HWE) were excluded. This was followed by data pooling for countries having more than one data set. To nullify the possible confounding effect of vaccinations disparity, country wise COVID-19 data of 16th January, 2021 (incidence and deaths per million of population) available to us before massive vaccination drive was used for Spearman's correlation analysis with minor allele frequency (MAF) of studied variants (in GraphPad Prism, version 5.0). A p value < 0.05 was considered significant.

Data for rs11549467 variant available from 74 studies affiliated to 34 countries, and rs11549465 from 111 studies belonging to 57 countries were finally enrolled. The MAF of rs11549467 ranged (0–10.8%), whereas that of rs11549465 ranged (0–25.7%) (Table 1). Since, HWE status of rs11549465 data retrieved from ALFRED database was unknown (which includes 29 studies for only rs11549465 from 19 countries), two separate correlation analysis (one by including ALFRED data under the assumption of their HWE obeyance or another by their complete exclusion) associating frequency distribution of HIF-1α variants with COVID-19 outcomes were conducted. ALFRED data was considered only when published genotype data were unavailable for a country. The results showed significant association of rs11549465 mutant allele with COVID-19 incidence, irrespective of inclusion ($p = 0.0156$, $r = 0.319$) or exclusion ($p = 0.0121$, $r = 0.403$) of ALFRED data. Further, mortality was found to be proportionately high (ALFRED data included: $p = 0.0547$, $r = 0.26$; excluded: $p = 0.084$, $r = 0.28$), although a statistically significant association could not be achieved. We did not find any association for rs11549467 with COVID-19 outcomes. Anticipating the confounding effect of altitudes of country and age of studied population, average elevation of country from sea level (Table 1) and available mean age data of enrolled studies (data not shown)

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Table 1 Country wise minor allele frequency (MAF) data of SNPs rs11549465 and rs11549467 of *HIF-1α* from healthy individuals

S. no	Country	Average altitude (in meter)	Covid-19 data (16th January 2021)		Genotype data (rs11549465)			Genotype data (rs11549467)		
			C/M	D/M	No. of studies	Total samples	MAF	No. of studies	Total samples	MAF
1	India	621	7600	110	1	103	0.097	3	405	0
2	Sri Lanka	228	2420	12	2	270	0.131	1	102	0
3	Nepal	3265	9078	66	1	59	0.076	–	–	–
4	Malaysia	538	4759	18	2	370	0.097	1	275	0.082
5	China	1840	61	3	17	6653	0.085	15	4664	0.108
6	Taiwan	1150	36	0.3	3	743	0.077	3	743	0.079
7	South Korea	282	1400	24	5	2438	0.044	2	316	0.038
8	Japan	438	2449	34	6	1726	0.053	5	1357	0.042
9	Vietnam	398	16	0.4	1	99	0.071	1	99	0.061
10	Israel	508	58,173	425	2	540	0.145	1	300	0.003
11	Bangladesh	85	3183	48	1	87	0.093	1	86	0
12	Pakistan	900	2315	49	1	96	0.12	1	96	0
13	Yemen	999	70	20	1	37	0.257	–	–	–
14	Palestine	305	29,346	329	1	51	0.15	–	–	–
15	Kazakhstan	387	8843	124	1	45	0.078	–	–	–
16	Kyrgyzstan	2988	12,608	210	1	28	0.107	–	–	–
17	Uzbekistan	450	2310	18	1	39	0.18	–	–	–
18	Cambodia	126	26	–	1	11	0.09	–	–	–
19	Laos	710	6	–	1	59	0.059	–	–	–
20	Poland	173	37,796	878	3	1175	0.075	2	850	0.028
21	Hungary	143	36,342	1168	1	345	0.133	–	–	–
22	Finland	164	7231	111	2	200	0.052	2	290	0.008
23	Turkey	1141	27,975	279	4	400	0.168	4	466	0.01
24	Spain	660	48,160	1140	2	577	0.111	4	868	0.015
25	Austria	910	43,447	781	1	2156	0.098	2	3094	0.017
26	Sweden	320	51,659	1019	1	258	0.091	1	256	0.018
27	France	375	43,961	1070	1	463	0.107	–	–	–
28	Italy	538	38,939	1346	1	107	0.187	1	107	0.009
29	UK	75	48,708	1282	2	139	0.09	2	235	0.013
30	Greece	498	14,224	521	1	124	0.069	–	–	–
31	Ireland	118	33,527	511	1	188	0.035	–	–	–
32	Portugal	372	51,910	839	1	736	0.125	2	152	0
33	Czech Republic	433	82,456	1326	–	–	–	1	219	0.021
34	Russia	600	24,283	446	2	2333	0.079	–	–	–

Table 1 (continued)

S. no	Country	Average altitude (in meter)	Covid-19 data (16th January 2021)		Genotype data (rs11549465)			Genotype data (rs11549467)		
			C/M	D/M	No. of studies	Total samples	MAF	No. of studies	Total samples	MAF
35	Belarus	170	23,661	166	1	28	0.089	–	–	–
36	Denmark	34	32,430	301	1	43	0.093	–	–	–
37	Estonia	61	27,649	241	1	1000	0.069	–	–	–
38	Moldova	139	37,793	801	1	32	0.141	–	–	–
39	Ukraine	175	26,490	475	1	29	0.052	–	–	–
40	USA	760	72,592	1210	3	2379	0.105	2	1460	0.006
41	Mexico	1111	12,415	1072	3	235	0.083	4	326	0.005
42	Colombia	593	36,544	935	1	94	0.069	2	177	0
43	Brazil	320	39,340	976	5	127	0	1	88	0.04
44	Peru	1555	31,789	1164	1	85	0.029	1	85	0
45	Mozambique	345	788	7	1	149	0.238	1	150	0.006
46	Guinea-Bissau	70	1243	23	1	82	0.08	1	82	0
47	Gambia	34	1589	52	1	113	0.049	1	113	0
48	Nigeria	380	514	7	2	207	0.022	2	207	0
49	Kenya	762	1821	32	1	99	0.045	1	99	0
50	Sierra Leone	279	367	10	1	85	0.029	1	85	0
51	Tanzania	1018	8	0.3	4	128	0.057	–	–	–
52	Democratic Republic of the Congo	726	227	7	2	34	0.028	–	–	–
53	Algeria	800	2335	64	1	30	0.1	–	–	–
54	Namibia	1141	11,650	109	1	7	0	–	–	–
55	Central African Republic	635	1020	13	2	56	0.01	–	–	–
56	Barbados	7	3603	24	1	96	0.036	1	96	0
57	Puerto Rico	261	29,647	591	1	104	0.144	1	104	0
58	Papua New Guinea	667	92	1	2	36	0	–	–	–
	Total	–	–	–	111	27,933	–	74	18,052	–

C/M cases/million, *D/M* deaths/million, *MAF* minor allele frequency, average elevation data of different countries from sea level was obtained from https://en.wikipedia.org/wiki/List_of_countries_by_average_elevation, https://www.worlddata.info and by individual search for a country

were also correlated with MAF and COVID-19 outcomes. However, no association was observed.

Significant association of rs11549465 mutant allele responsible for enhanced HIF-1α activity with COVID-19 susceptibility suggest HIF-1α signaling in SARS-Cov2 infection to be crucial. Study on isolated monocytes or monocytes from severe COVID-19 patients also has revealed escalated SARS-Cov2 infection under high glucose level in dose-dependent rise of HIF-1α activity [4]. Interestingly, proteome analysis of SARS-Cov2 infected cells document enhanced HIF-1α signaling [4, 7]. Further, enhanced HIF-1α activity is demonstrated in other RNA virus infection independent to hypoxia [2, 8]. Although hypoxia stimulated upregulated HIF-1α activity is described to inhibit SARS-Cov2 infection by reducing expression of host receptors for viral entry in experimental studies [1, 5, 9], these receptors being required for normal physiology; we hypothesize that their basal expression in normal oxygen level may facilitate viral infection, and hypoxia in established SARS-Cov2 infection may be detrimental. Documentary evidences supporting this hypothesis are warranted. Moreover, the beneficial role of pre-existing chronic hypoxia against COVID-19 is suggested to be due to HIF-2α activity [10], which is often antagonistic in action to HIF-1α [2]. However, lack of association of average elevation data of countries with COVID-19 outcomes and HIF1-α MAF distribution challenge the definitive protective role of high altitude against COVID-19. HIF-1α being a strong inducer for glycolytic pathway and pro-inflammatory cytokine expression [1–4]; enhanced HIF-1α activity may be vital for viral replication leading to viral load and cytokine storms, the two important determinants for COVID-19 mortality. Although we did not find significant association with mortality (which could be due to low MAF and small sample size), comparative study on HIF-1α activity, viral load and cytokines level in diabetic and non-diabetic COVID-19 patients may provide further insight into the mechanism of HIF-1α signaling in COVID-19 complications. Besides, rs11549465 mutant being a potential risk factor of cancer incidence [6], it may contribute to certain extent for COVID-19 associated increased severity and mortality in cancer patients [11]. We recommend large sample case–control studies for the validation of results.

Acknowledgements We acknowledge our Vice Chancellor, Prof K. K Basa for his encouragement and support of DST-FIST to our Department at Maharaja Sriram Chandra Bhanjadeo University. We also thankfully acknowledge the authors whose contribution have been cited.

Author contributions GD: conceived the original idea, analyzed the data, wrote the final draft of manuscript; AD: collected data and performed preliminary data analysis, prepared the pre-draft; MP: collected data and performed preliminary data analysis.

Funding We did not receive a fund of any kind concerning to this work.

Declarations

Conflict of interest All authors declare no conflict of interest.

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