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Genetic Variants predisposition to Severe COVID-19 Illness Identified in a Healthy Nigerian Man, using Nebula Genomics Gene.iobio Platform

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ABSTRACT

Background: The landscape of coronavirus disease in Nigeria is very undulating with established uncertainty due to blatant disregard to genomics research by government health care institutions. As other countries in the west are documenting Covid-19 disease genomics variations among her populace, few research efforts are made by a private university to replicate such data in Nigeria. The objective of this case study was to identify genetic variations associated with severe Covid-19 disease, by whole genome sequencing on a heathy adult Nigerian. **Methods**: Buccal swabs were self-collected and DNA extracted, quantified, normalised before sequencing on the high-throughput MGI DNBSEQ-T7 DNA sequencer using Nebula genomics platform. Raw sequences in FASTQ files were assembled in contigs or chromosomes using the Gene iobio pipeline. DNA sequences were aligned with integrated genome viewer (IGV) to the human reference genome GRCh38 (hg38) for single nucleotide polymorphism (SNP) variant calls, deletions and insertions. The genetic variations were compared with the recent genome wide association study (GWAS) implicating 8 genetic loci associated with critical covid-19 disease. **Results**: Five (5) out of the eight (8) genetic variants associated with severe covid-19 were identified in the healthy subject. The highest number of SNPs occurred in Leucine Zipper Transcription Factor Like 1 (LZTFL1) with 147 SNPs, followed by 100 SNPs observed in Oligoadenylate synthetase 1 (OAS1). Six (6) missense variants were observed in Coiled-Coil Alpha-Helical Rod Protein 1 (CCHCR1), all occurring in heterozygous pattern. The SNP in rs3131294 for variant Notch receptor 4 (NOTCH4) located at chr6:32220606 was present in 90% of the allele frequency, while the variant found in Dipeptidyl peptidase (DPP9) on rs2109069 located in chr19:4719431 implicated in GWAS and in this case study had 38% allele frequency. **Conclusion**: This case study has demonstrated the importance of genomics study that has the potential to play significant roles in mitigating risk factors associated with severe covid-19 disease for public health advise and personalized medicine.

Keywords: genetics, variants, covid-19, severe, healthy, GWAS, SARS-CoV-2
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INTRODUCTION

Covid-19 or SARS-CoV-2 has caused significant number of mortalities amounting to over 1.7 million globally, since the outbreak in December, 2019. Nigeria has recorded over 84,414 confirmed cases as at December 28, 2020 (https://covid19.ncdc.gov.ng/). Genome wide association studies (Not done yet in Nigeria) have consistently identified potential genetic regions that may lead to predispositions in developing critical or severe covid-19 illness with respiratory failure (**1**). While majority of people who get infected presents with mild symptoms such as fever, loss of taste or smell, cough and breathing with difficulty, a small number, less than 5% will develop severe illness leading to multi-organ failure, septic shock and respiratory failure (**2**). Recently, a genome-wide association study (GWAS) that involved 2,244 individuals of European, South Asian, East Asian, or African ancestry has identified 8 regions of the human genome that may be linked with severe illness of Covid-19 (**3**). These 8 regions codes for genes such as IFNAR2, OAS1-3, CCHCR1, TYK2, LZTFL1, HLA-G, NOTCH4 and DPP9) that are responsible for the normal functioning of the immune system.

Regrettably, most of the GWAS focus on Africa Americans and not populations from sub-Saharan Africa. Reports had it that 81% of all GWAS collections are from people of European ancestry, while 14% are from East Asia ancestry (**4**), thus leaving Nigerians that constitutes 25% of African population behind. This apparent lack of inclusion will continue to increase the lacuna disparities in genomics health information as relevant genetics-risk associations in Nigeria will not be captured early (**5**).

In terms of SARS-COV-2 sequencing contribution to the global database, Nigeria has submitted only one complete genome sequence (MT576584.1-SARS-CoV-2/human/NGA/NG57752/2020), out of over 30,091 as at December 17, 2020 (https://www.ncbi.nlm.nih.gov/datasets/coronavirus/genomes/) There is no information on the database of genome sequence of individuals infected with either mild or severe covid-19 disease. Besides, only few isolated Nigerians (both healthy and disease-associated) have sequenced their full genome to date. The purpose of this case study was to use available genome data recently sequenced from a healthy Nigerian to search for the presence of genetic variants associated with severe covid-19 illness.

METHODS

Sample collection and DNA extraction: Two buccal swabs were collected following the Nebula Genomics sample collection instructions (https://nebula.org). DNA was extracted from buccal swabs using the phenol-free Nucleon BACC Genomic DNA Extraction Kits with proprietary resin added following cell lysis, deproteinization with sodium perchlorate, and a single chloroform extraction. DNA samples were re-suspended in 1 ml TE buffer pH 7.5 (10mM Tris-Cl pH 7.5, 1mM EDTA pH 8.0). The yield of the DNA was measured using Qubit (Thermofischer) and normalised to 50ng/µl before sequencing.

Genome sequencing: High-throughput MGI DNBSEQ-T7 DNA sequencing machines was used for generating 150 bp paired-end reads, sequencing 30X and were confirmed with Illumina NovaSeq 6000 whole genome sequencing platform.

Bioinformatics: The raw sequences in FASTQ files were assembled in contigs representing the chromosomes on Gene iobio

pipeline. The compressed in BAM file was converted to CRAM file for genome reconstruction and indexing datasets. DNA sequences were aligned to the human reference genome GRCh38 (hg38) and variant calls and mutations were accomplished with VCF files on the Gene.iobio pipeline **(6)**. The Integrated Genomics Viewer (IGV) was used for visualizing the genome (**7**).

RESULTS

The sequencers generated over 50GB (Gigabase) Forward and 50GB Reverse of the DNA in FASTQ files. GWAS identified 4 chromosomes (red colour) that harbour the location of the genes that have been associated with severe COVID-19 illness in this case study (**Figure 1**).

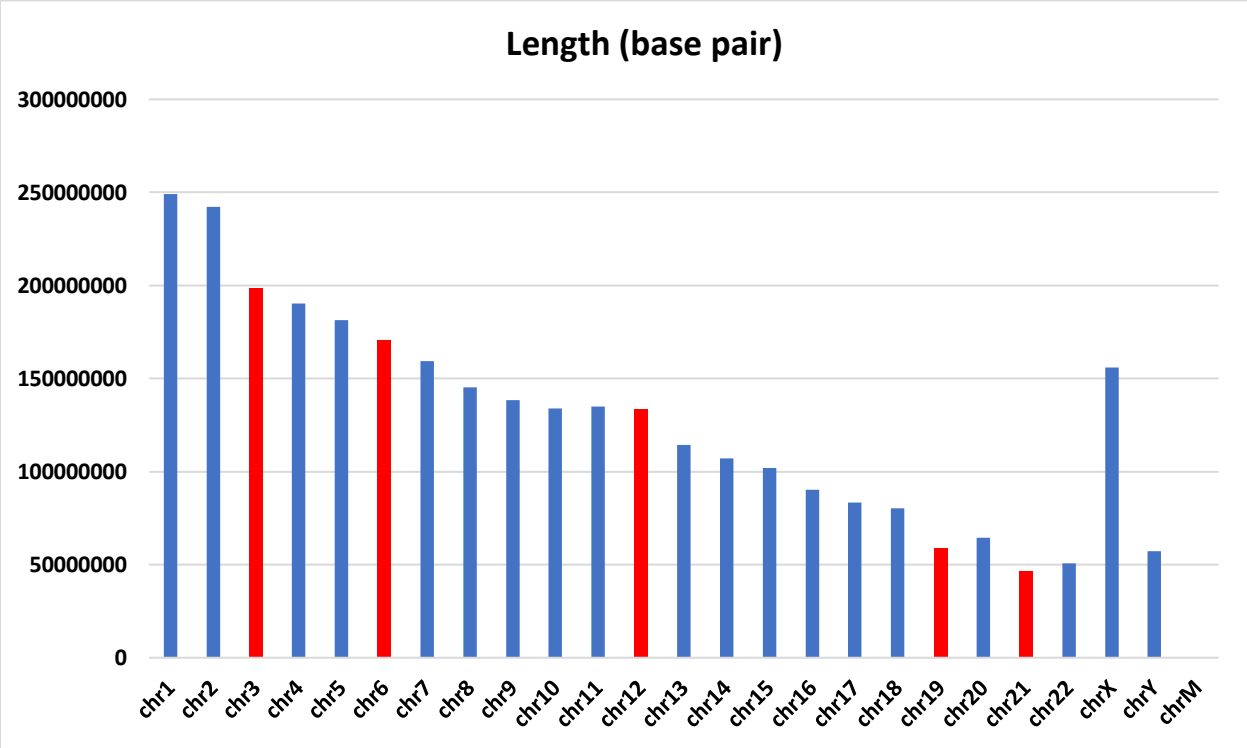

Figure 1: GWAS identified 4 chromosomes (red colour) that harbour the location of the genes associated with severe COVID-19 illness.

Table 1: shows the gene name, location in the chromosome, number and type of genetic variations with reference to the human genome (GRCh38).

Gene	Gene name	Chromosome Loci	SNPs	Deletions	Insertions
TYK2	Tyrosine kinase 2	chr19 10,350,529 - 10,380,676	70	14	6
LZTFL1	Leucine Zipper Transcription Factor Like 1	chr3 45,823,316 - 45,916,042	147	20	11
HLA-G	Human Leukocyte Antigen-G	chr6 29,826,967 - 29,831,125	55	2	2
CCHCR1	Coiled-Coil Alpha-Helical Rod Protein 1	chr6 31,142,439 - 31,158,238	95	3	6
NOTCH4	Notch Receptor 4	chr6 32,194,843 - 32,224,067	72	13	8
OAS1	Oligoadenylate synthetase 1	chr12 112,906,777 - 112,933,222	100	4	2
OAS2	Oligoadenylate synthetase 2	chr12 112,978,395 - 113,011,723	60	4	3
OAS3	Oligoadenylate synthetase 3	chr12 112,938,352 - 112,973,249	49	5	5
DPP9	Dipeptidyl peptidase 9	chr19 4,675,224 - 4,724,673	56	9	10
IFNAR2	Interferon receptor 2	chr21 33,229,901 - 33,265,675	39	6	9

Table 1 shows the gene name, location in the chromosome, and type of genetic variations with reference to the human genome (GRCh38). The highest number of SNPs (Single Nucleotide Polymorphism) occurred in LZTFL1 with 147 SNPs, followed by 100 SNPs in OAS1. **Table 2** shows the alleles associated with covid-19 severity (imputed from the 1000 genomes project datasets that have frequency above 5%) and the paternal/maternal genotypes identified in the Nigerian man, indicating that this individual has 5 out of the 8 genes representing 62.5% probability of developing critical covid-19 if perhaps he gets infected with SARS-COV-2.

Table 2: Alleles associated with severe Covid-19 illness in this case study (highlighted in colour)

Gene loci	Variant ID	Human GRCh38/hg38 Assembly	Allele associated with COVID-19 severity	Effect size/odds ratio	Approximate effect allele frequency	Paternal/ Maternal genotype	Statistical Significance
LZTFL1	rs73064425	chr3:45859597	T	0.74	15%	C/C	4.80X10-30
CCHCR1	rs143334143	chr6:31153649	A	0.64	12%	G/A	8.80X10-18
DPP9	rs2109069	chr19:4719431	A	0.34	38%	G/A	4.00X10-12
OAS1/3	rs10735079	chr12:1129422	A	0.26	68%	A/A	1.60X10-8
TYK2	rs74956615	Chr19:1031704	A	0.47	8%	T/T	2.30X10-8
NOTCH4	rs3131294	chr6:32220606	G	0.41	90%	G/G	2.80X10-8
HLA-G	rs9380142	Chr6:29831018	A	0.26	74%	A/A	3.20X10-8
IFNAR2	rs2236757	Chr21:3325261	A	0.26	34%	G/G	5.00X10-8

Note: Red colour shows heterozygous SNP variants in the individual, while green colours are those variants that occurred in a homozygous pattern. No colour shows SNP variants that did not occur in the case study.

In-debt analysis using gene.iobio pipeline shows that this individual has other genetic variations in the chromosomes. For example, **Table 3** shows selected variations indicating type of zygosity, pathogenicity, population frequency and conservation. Missense variant was observed in OAS1, whereby, the SNP (Guanine to Adenine) led to a change in the amino acid translation from Glycine to Arginine at position 397. A synonymous variant was observed in OAS2 rs1694224 located at 113006480 (**Figure 2**) in GRCH38 with (C to T) SNP without any error reading in the translation to serine at 512 position. The missense variation was found to be homozygous and not conserved. Similar observation was noted in SNP variant (**G to A**) rs1859330 at chr12: 112938583 for OAS3 (**Figure 3**) with missense translation from Arginine to Lysine at position 18. Out of 147 SNPs identified in LZTFL1 gene, only one missense was observed at rs77717940 with a corresponding translation from Lysine to Glutamine at position 229.

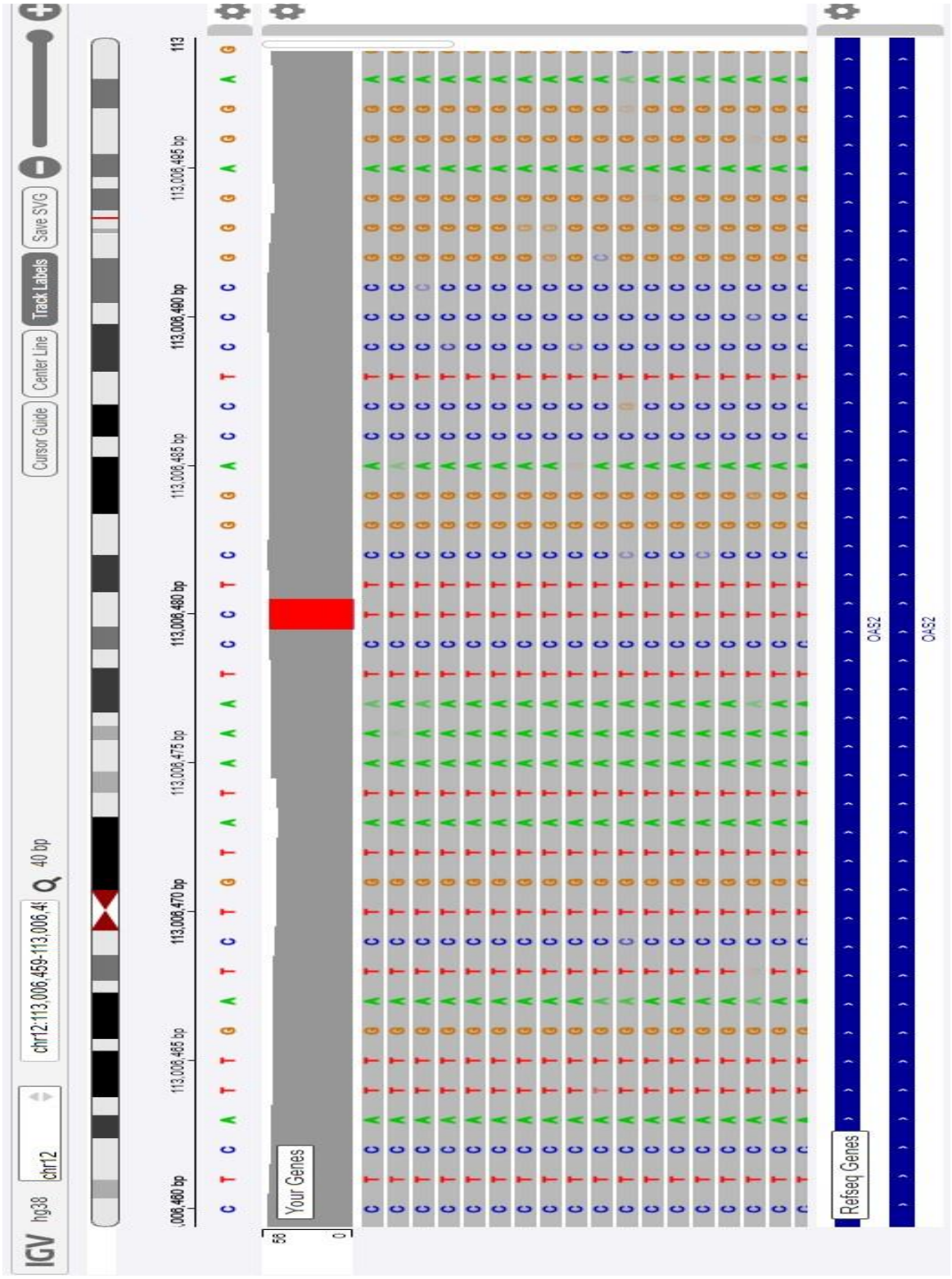

Figure 2: A synonymous SNP variant (**C to T**) observed in OAS2 rs1694224 located at Chr12:113006480 in this case study.

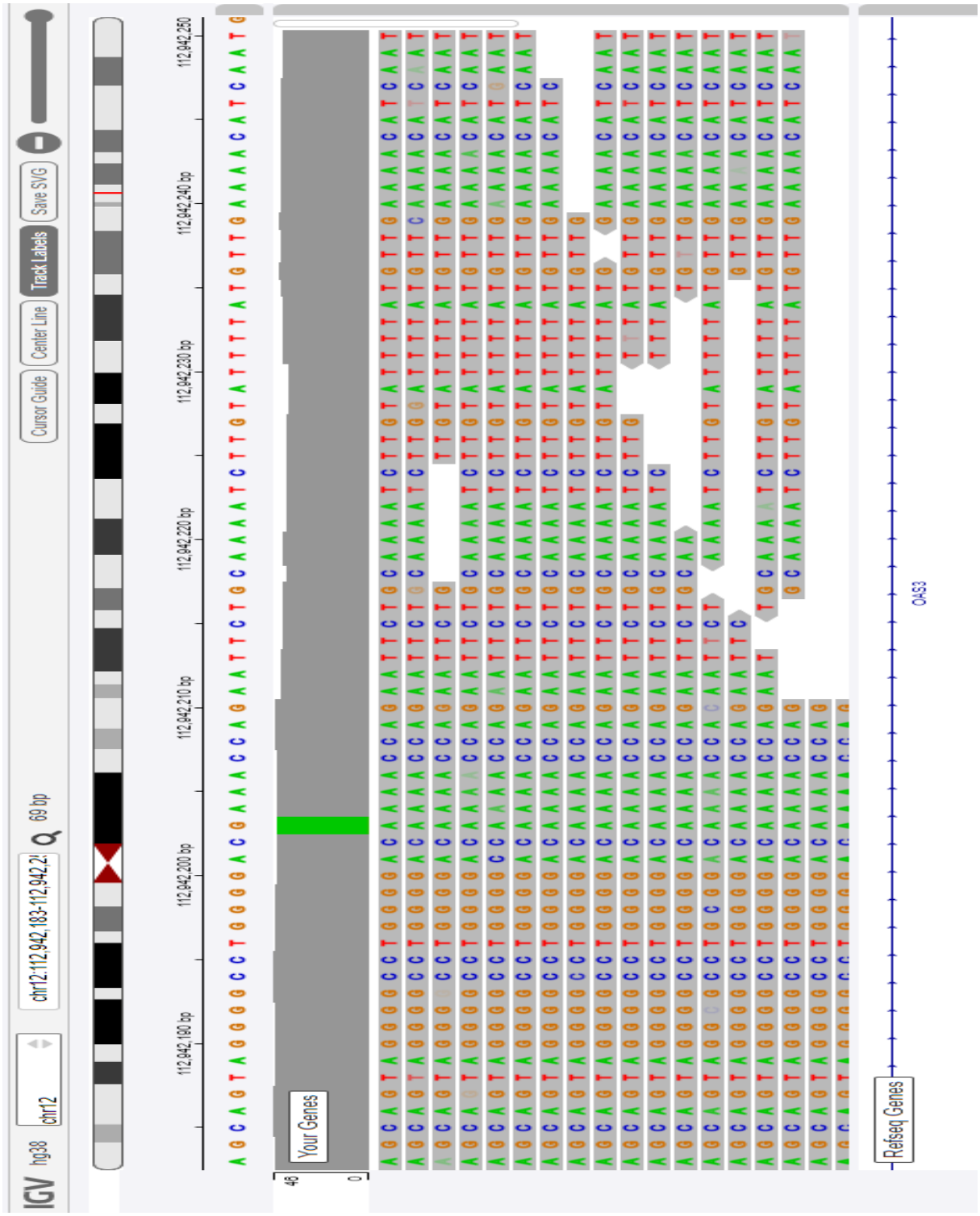

Figure 3: SNP variant (**G to A**) in rs1859330 at chr12: 112938583 for OAS3 with missense translation from Arginine to Lysine at position 18.

Table 3: shows selected variations indicating type of zygosity, pathogenicity, population frequency and conservation

Genes identified.	Selected variant	Ref Seq	Chr	Location	Variant type	Changes in amino acid	Zygosity	Pathogenicity	Population frequencey	Conservation
Variant in TYK2	SNP (70)	rs12720276	19	10361881	A->C	Pro at 616	Heterozygous	Synonymous variant	3% Allele frequency	Highly conserved
		rs280519	19	10362257	A->G		Homozygous	Splice region variant, int	52% Allele frequency	Not conserved
		rs280520	19	10362462	A->G		Heterozygous	Splice region variant, int	28% Allele frequency	Not conserved
		rs139290454	19	10349712	C->T		Heterozygous	Downstream gene varian	3% Allele frequency	Marginally conserved
	Insertions (6)	rs143429818	19	10359067	A->AAAAC		Homozygous	Intron variant	12% Allele frequency	Not conserved
	Deletions (14)	rs12720308	19	10356765	CA->C		Heterozygous	Intron variant	3% Allele frequency	Marginally conserved
Variant in OAS1	SNP (100)	rs2660	12	112919637	G->A	Gly to Arg at 397	Homozygous	**Missense variant**	75% Allele frequency	Not conserved
		rs1015542	12	112906341	C->G		Homozygous	Upstream gene variant	85% Allele frequency	Marginally conserved
	Deletion (4)	rs35847220	12	112923901	CA->C		Homozygous	Downstream gene varian	75% Allele frequency	Moderately conserved
	Insertions (2)	rs142136498	12	112924466	T->TTA		Homozygous	Downstream gene varian	75% Allele frequency	Marginally conserved
Variant in OAS2	SNP (60)	rs2384075	12	112978848	G->A		Homozygous	Intron variant	34% Allele frequency	ND
		rs1293755	12	112997645	A->T	Val at 251	Homozygous	Synonymous variant	79% Allele frequency	ND
		rs16942424	12	113006480	C->T	Ser at 512	Homozygous	Synonymous variant	3% Allele frequency	ND
	Deletions (4)	rs60033508	12	112993962	TGG->T		Homozygous	Intron variant	80% Allele frequency	ND
	Insertions (3)	rs143020646	12	113001389	C->CAT		Homozygous	Intron variant	79% Allele frequency	ND
Variant in OAS3	SNP (49)	rs1859330	12	112936583	G->A	Arg to Lys at 18	Homozygous	**Missense variant**	64% Allele frequency	ND
		rs1859329	12	112938647	C->T	Ala at 39	Homozygous	Synonymous variant	75% Allele frequency	ND
		rs2285932	12	112949145	T->C	Ile at 438	Homozygous	Synonymous variant	78% Allele frequency	ND
	Deletions (5)	rs796874414	12	112945315	GAAA->G		Homozygous	Intron variant	38% Allele frequency	ND
	Insertions (5)	rs371197275	12	112972879	G>GGTGTGT		Homozygous	3 prime utr variant	6% Allele frequency	ND
Variant in LZTFL1	SNPs (147)	rs77717940	3	45828531	T->C	Lys to Glu at 229	Heterozygous	**Missense variant**	0.3% Allele frequency	Moderately conserved
		rs4683144	3	45822764	T->C		Homozygous	Downstream gene varian	86% Allele frequency	Marginally conserved
	Deletions (20)	rs5848772	3	45844090	ATAT->A		Heterozygous	Upstream gene variant	55% Allele frequency	Not conserved
	Insertions (11)	rs10656359	3	45839093	A->ATTC		Homozygous	Intron variant	82% Allele frequency	Marginally conserved

Table 4: Shows missense translations in CCHCR1 SNP variants all occurring in heterozygous pattern.

Genes identified.	Selected variant	Ref Seq	Chr	Location	Variant type	Changes in amino acid	Zygosity	Pathogenicity	Population frequencey	Conservation
Variant in HLA-G	SNPs (55)	rs12722477	6	29826599	C->A	Leu to Ile at 139	Homozygous	**Missense variant**	14% Allele frequency	Not conserved
		rs1630223	6	29827659	G->A	Ala at 10	Homozygous	Synonymous variant	48% Allele frequency	Marginally conserved
		rs1630165	6	29827880	G->A	Leu at 17	Homozygous	Synonymous variant	48% Allele frequency	Not conserved
		rs80153902	6	29828141	G->A	Gln at 61	Heterozygous	Synonymous variant	0.5% Allele frequency	Marginally conserved
		rs1130355	6	29828216	G->A	Pro at 86	Homozygous	Synonymous variant	48% Allele frequency	Marginally conserved
		None	6	29829671	G->A	Pro at 296	Heterozygous	Synonymous variant	6% Allele frequency	Not conserved
		rs1130363	6	29829919	A->G	Arg at 338	Homozygous	Synonymous variant	54% Allele frequency	Marginally conserved
	Deletions (2)	rs551170211	6	29827589	TC->T		Heterozygous	Intron variant	0.4% Allele frequency	Marginally conserved
	Insertions (2)	rs3215482	6	29828349	A->AC		Homozygous	Intron variant	49% Allele frequency	Not conserved
Variant in DPP9	SNPs (56)	rs57034092	19	4695372	G->T		Heterozygous	Splice region variant, intr	7% Allele frequency	Highly conserved
		rs10425839	19	4676128	T->G		Heterozygous	3 prime utr variant	39% Allele frequency	Moderately conserved
		rs7255543	19	4724720	G->T		Homozygous	Upstream gene variant	70% Allele frequency	Not conserved
	Deletions (9)	rs72096635	19	4674665	GCC->G		Heterozygous	Downstream gene varian	11% Allele frequency	Marginally conserved
	Insertions (10)	rs59514816	19	4680412	G->GAAAAAC		Heterozygous	Intron variant	43% Allele frequency	Marginally conserved
Variant in CCHCR1	SNPs (95)	rs1576	6	31142614	G->C	Ser to Cys at 865	Heterozygous	**Missense variant**	28% Allele frequency	Not conserved
		rs150789792	6	31143314	T->A	Gln to Leu at 756	Heterozygous	**Missense variant**	0.7% Allele frequency	Marginally conserved
		rs73397100	6	31143348	G->A	Arg to Cys at 745	Heterozygous	**Missense variant**	1% Allele frequency	Marginally conserved
		rs130072	6	31144707	C->T	Arg to Gln at 716	Heterozygous	**Missense variant**	8% Allele frequency	Highly conserved
		rs130068	6	31148469	G->A	Arg to Trp at 506	Heterozygous	**Missense variant**	44% Allele frequency	Marginally conserved
		rs72856718	6	31157480	C->A	Glu to Ter at 41	Heterozygous	Stop gained	9% Allele frequency	Highly conserved
Variant in NOTCH4	SNPs (72)	rs422951	6	32220606	T->C	Thr to Ala at 320	Heterozygous	**Missense variant**	40% Allele frequency	Not conserved
		rs520692	6	32220863	T->C	Asp to Gly at 272	Heterozygous	**Missense variant**	29% Allele frequency	Not conserved
		rs915894	6	32222613	T->G	Lys to Gln at 117	Homozygous	**Missense variant**	36% Allele frequency	ND
	Deletions (13)	rs35795312	6	32223881	TAGC->T	LeuLeu to Leu at 15-16	Homozygous	Inframe deletion	34% Allele frequency	ND
	Insertions (8)	rs3216791	6	32220659	G->GCC		Heterozygous	Intron variant	29% Allele frequency	ND
Variants in IFNAR2	SNPs (39)	rs2248412	21	33233226	A->G		Heterozygous	Intron variant	15% Allele frequency	ND
	Deletions (6)	rs1490131675	21	33249343	CAAA->C		Homozygous	Intron variant	48% Allele frequency	ND
	Insertions (9)	None	21	33237078	G->GGTGTGTGT		Heterozygous	Intron variant	3% Allele frequency	ND

The highest number of missense translations was observed in CCHCR1 as shown in **Table 4** all occurring in heterozygous pattern. The SNP that occurred in variant ID for CCHCR1 rs143334143 at chr6:31153649 implicated in

the covid-19 severity as visualized with IGV is presented in **Figure 4**.

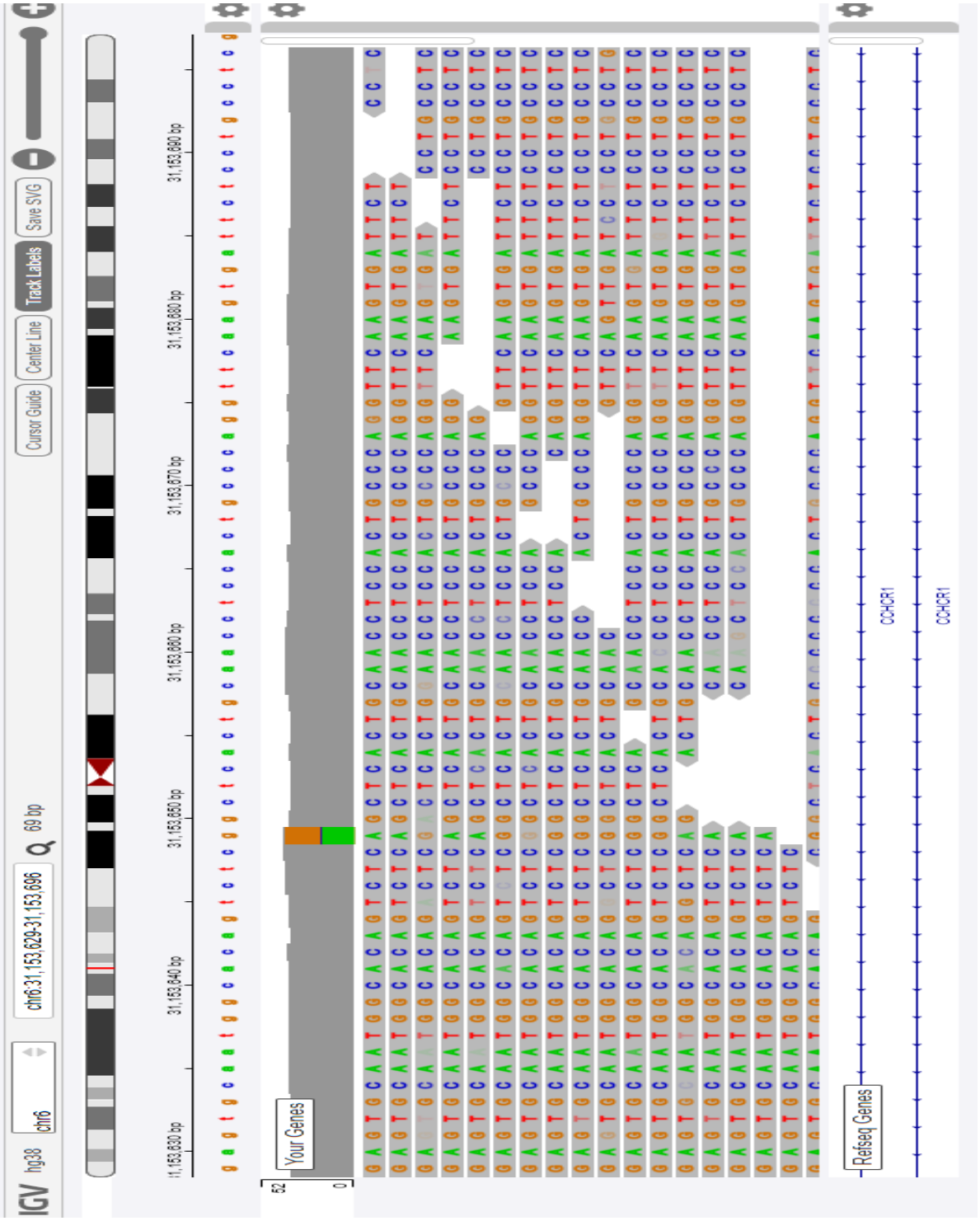

Figure 4: SNP variant for CCHCR1 rs143334143 at chr6:31153649

Interestingly, one in-frame deletion in NOTCH4 variant rs35795312 led to reduction on the number amino acids at position 15-16 as shown in table 4. The SNP in rs3131294 for NOTCH4 located at chr6:32220606 was present in 90% of the allele frequency. The variant found in DPP9 on rs2109069 located in chr19:4719431 (**Figure 5**) implicated in covid-19 severity and in this case study had 38% allele frequency

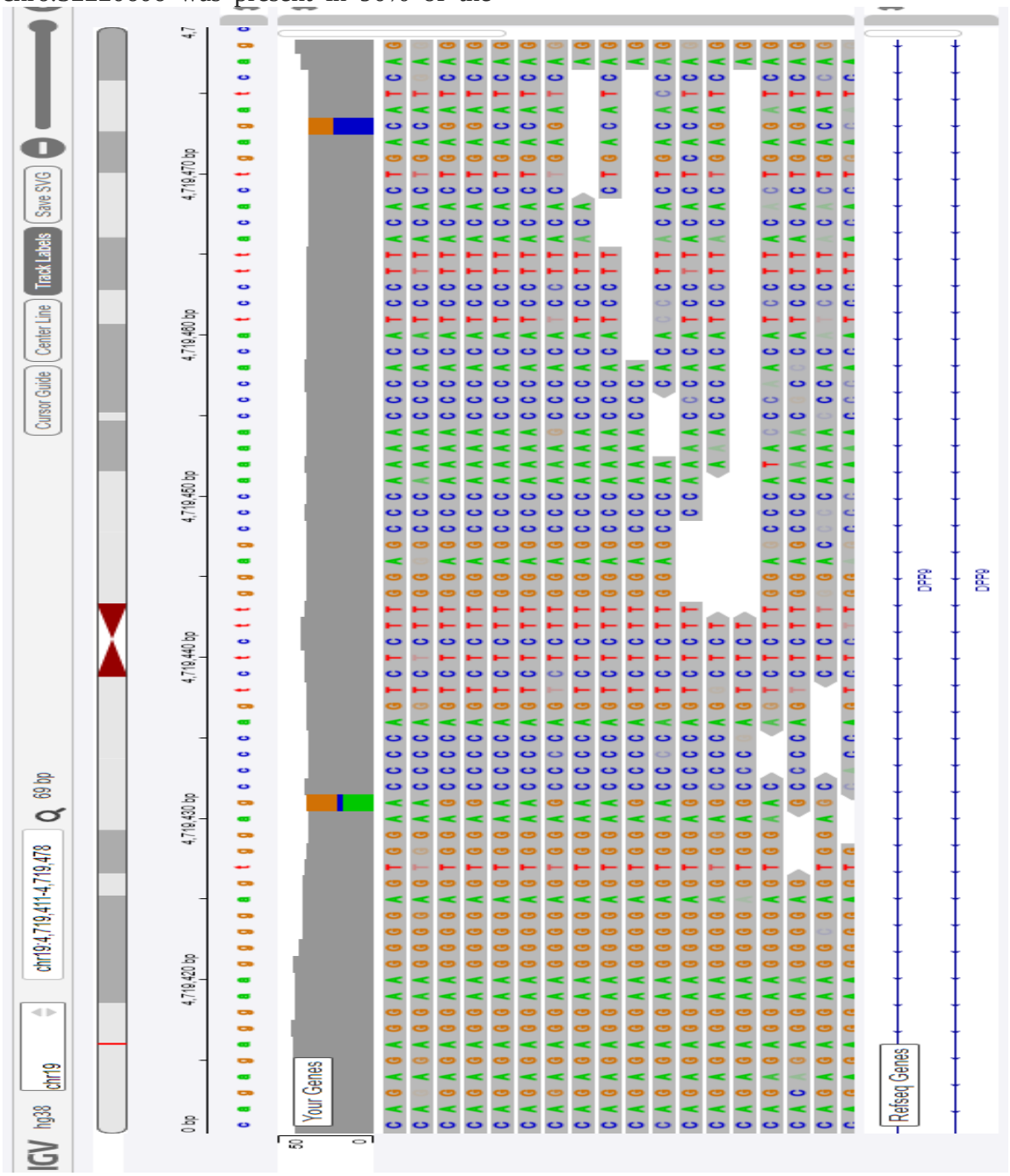

Figure 5: Variant in DPP9 on rs2109069 SNP (**G to A**) located in chr19:4719431

DISCUSSIONS

To our knowledge, this is the first case study identifying genetic variations associated with severe or critical covid-19 disease in a healthy non-Covid-19, adult Nigerian. It is very important to note that the variations observed in this healthy individual may not necessarily translate to having severe covid-19 disease. There are many factors that play significant roles in the development of severe covid-19. The case study had only 62.5% chance for the variants identified in the GWAS. However, the individual has other variants that may down-regulate the expressions of the implicated SNPs. For example, the SNPs observed in IFNAR2 and TYK2 in the GWAS study on severity of COVID-19 did not occur in this case study and therefore may not have effect on the subject. This is based on the fact that the Mendelian randomisation results obtained in the GWAS implying a causal role for interferon receptor 2 (IFNAR2) and Tyrosine kinase 2 (TYK2) are involved in innate antiviral defences, which are known to be important early covid-19 severity. The TYK2 gene is associated with the cytokine storm that is responsible for most deaths in younger people. This was statistically significant in their transcriptome confirmatory analyses (**3**). In contrast, the variant rs10735079 (chr12, $p = 1.60 \times 10\text{-}8$) that has adenine allele associated with covid-19 severity is located in the vicinity of interferon inducible oligoadenylate synthetase (OAS) gene cluster (OAS1, OAS2 and OAS3). This cluster is involved in the antiviral restriction enzyme activation. This individual acquired the allele (A) from both parents with 68% frequency. Previous studies conducted in 2006 have implicated this gene loci to SARS-CoV in China (**8**).

Dipeptidyl peptidase (DPP9) found in chromosome 19 had 56 SNPs. The variant gene in rs57034092 had a splice region variant-intron variant which is highly conserved and it has been hypothesized to play a role in apoptosis, proliferation, interaction with the extracellular matrix, and regulation of the immune response (**9**). The variant rs2109069 located in chr19:4719431 implicated in this case study had 38% allele frequency, might be very important role in disease susceptibility as previous studies, though not related to covid-19 have implicated DPP9 in leukemia (**10**), non-small cell lung cancer (**11**), and ovarian cancer (**12**). We have demonstrated in our previous *in silico* study (**13**), how the S (spike) protein binding with the human protein CD209 molecule, which is a pathogen-recognition receptor that is expressed on the surface of immature dendritic cells (DCs) and is involved in initiation of primary immune response, may probably inactivate the CD209 molecule. As numerous evidences suggest that genetic factors may likely influence the onset and progression of infectious diseases (**14**), the evidence for Covid-19 disease is just emerging. Age (over 60 years), male gender, and the presence of concomitant metabolic conditions such as obesity, diabetes, and hypertension have been demonstrated (**15**; **16**).

CONCLUSION: Knowledge from this information with genomics studies and GWAS on susceptibility of an individual or cohorts of people , can provide an insight on how to mitigate risk factors associated with covid-19 infection. However, interpretation of genetic polymorphisms in individuals must be taken with cautious optimism.

Conflict of interest: None to declare.

REFERENCES

1.Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A et al. Genome-wide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020;383(16):1522-1534. doi: 10.1056/NEJMoa2020283

2.Renu K, Prasanna PL, Valsala Gopalakrishnan A. Coronaviruses pathogenesis, comorbidities and multi-organ damage - A review. *Life Sci*. 2020;255:117839. doi:10.1016/j.lfs.2020.117839

3.Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in Covid-19. *Nature*. 2020;10.1038/s41586-020-03065-y.

4.Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature 2016;538:161-4

5.Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. Nature genetics 2019;51:584

6.Ekawade A, Velinder M, Ward A, DiSera T, Marth G. genepanel.iobio - an easy to use web tool for generating disease- and phenotype-associated gene lists. bioRxiv 722843 (2019) doi:10.1101/722843.

7.Robinson JT, Thorvaldsdóttir H, Turner D, Mesirov JP. igv.js: an embeddable JavaScript implementation of the Integrative Genomics Viewer (IGV). bioRxiv 2020.05.03075499.

8.He J, Feng D, Vlas SJ de, Wang H, Fontanet A, Zhang P, et al. Association of sars susceptibility with single nucleic acid polymorphisms of oas1 and mxa genes: A case-control study. BMC infectious diseases, 2006; 6, 106

9.Zhang H, Chen Y, Keane FM, Gorrell MD. Advances in understanding the expression and function of dipeptidyl peptidase 8 and 9. Mol Cancer Res. 2013;11:1487–96.

10.Johnson DC, Taabazuing CY, Okondo MC, Chui AJ, Rao SD, Brown FC, et al. DPP8/DPP9 inhibitor-induced pyroptosis for treatment of acute myeloid leukemia. Nat Med. 2018;24:1151–56

11.Tang Z, Li J, Shen Q, Feng J, Liu H, Wang W, et al. Contribution of upregulated dipeptidyl peptidase 9 (DPP9) in promoting tumoregenicity, metastasis and the prediction of poor prognosis in non-small cell lung cancer (NSCLC). Int J Cancer. 2017;140:1620–32

12.Smebye ML, Agostini A, Johannessen B, Thorsen J, Davidson B, Trope CG, et al. Involvement of DPP9 in gene fusions in serous ovarian carcinoma. BMC Cancer. 2017;17:642

13.Anukam KC, Uche OK. In silico Prediction of Binding Site Residues on Coronavirus Disease (COVID19) Structural Proteins for Potential Drug Targets and Human Host Interactome Using Proteome Database. J Med Lab Sci, 2020; 30 (1): 42-67

14.Hill AVS. Evolution, revolution and heresy in the genetics of infectious disease susceptibility. Philos Trans R Soc Lond B Biol Sci. 2012; 367(1590): 840–849 2012;367(1590):840–849. doi: 10.1098/rstb.2011.0275

15.Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents. 2020;34(2):339-343. doi: 10.23812/Editorial-Conti-3.

16.Watanabe M, Risi R, Tuccinardi D, Baquero CJ, Manfrini S, Gnessi L. Obesity and SARS-CoV-2: A population to safeguard. Diabetes Metab Res Rev. 2020:e3325. doi: 10.1002/dmrr.3325.