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Short Communication

Insights into disease resilience and longevity: Hints from COVID-19 recovered nonagenarians and centenarians

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ABSTRACT

The effects of aging on the organism manifest in various ways, including profound and complex changes in functioning patterns, responses to stimuli, and regenerative capacity. Nevertheless, it is remarkable that some elderly individuals maintain their health and functionality despite advanced age, showing resilience to environmental adversities, such as SARS-CoV-2 infection. In this study, we examined a unique cohort of 100 individuals older than 90 years, including centenarians, who recovered from COVID-19 before the availability of vaccines in Brazil. We performed whole-exome analyses and identified incidental findings in four participants. These findings included pathogenic variants associated with serious conditions, such as cancer predisposition and cardiovascular diseases. Specifically, variants were found in the *RYR1*, *DSP*, *BRCA2*, *BRCA1*, and *TTN* genes. Also, other two individuals were homozygous for rare variants in the *TYK2* gene, related to primary immunodeficiencies. The significance of these findings is underscored by the fact that, despite carrying these rare variants, these individuals surpassed 90 years of age and survived the COVID-19 pandemic. This suggests the presence of genetic protective factors that contribute to longevity and resilience. Therefore, this study provides new insights into interpreting incidental findings in long-lived populations and raises important questions for clinical practice and the genetics of longevity.

1. Introduction

The COVID-19 pandemic has disproportionately affected older adults, leading to higher rates of morbidity and mortality in this population (Mueller et al., 2020; Lebrasseur et al. 2021; Cocuzzo et al., 2022). In this sense, the elderly usually have a higher prevalence of comorbidities such as cardiovascular diseases, diabetes, and chronic respiratory conditions, which increase their vulnerability to severe outcomes from COVID-19 (Dessie and Zewotir, 2021; Dai et al., 2021; Péterfi et al., 2022).

Additionally, the aging immune system, characterized by immunosenescence and chronic low-grade inflammation (inflammaging), results in a diminished ability to mount effective immune responses against infections (Witkowski et al., 2022; Napoli et al., 2023; Zinatizadeh et al., 2023). The combination of these factors makes the elderly more susceptible to severe disease progression, complications, and death when infected by SARS-CoV-2. However, there were many cases of unvaccinated centenarians who had a silent infection or recovered from mild

Abbreviations: ACMG, American College of Medical Genetics and Genomics; BQSR, Base Quality Score Recalibration; COVID-19, Coronavirus Disease 2019; CADD, Combined Annotation Dependent Depletion; COPD, Chronic Obstructive Pulmonary Disease; DNA, Deoxyribonucleic Acid; DSP, Desmoplakin; EDTA, Ethylenediaminetetraacetic Acid; IFIH1, Interferon Induced With Helicase C Domain 1; IFN, Interferon; IFNAR1, Interferon Alpha And Beta Receptor Subunit 1; IFNAR2, Interferon Alpha And Beta Receptor Subunit 2; IRF7, Interferon Regulatory Factor 7; IRF9, Interferon Regulatory Factor 9; iPSC, Induced Pluripotent Stem Cells; MYD88, Myeloid Differentiation Primary Response 88; RYR1, Ryanodine Receptor 1; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; STAT1, Signal Transducer And Activator Of Transcription 1; STAT2, Signal Transducer And Activator Of Transcription 2; TICAM1, Toll-Like Receptor Adaptor Molecule 1; TLR3, Toll-Like Receptor 3; TLR7, Toll-Like Receptor 7; TTN, Titin; TYK2, Tyrosine Kinase 2; UNC93B1, Unc-93 Homolog B1; VUS, Variant of Uncertain Significance; WES, Whole-Exome Sequencing; WGS, Whole-Genome Sequencing; WHO, World Health Organization.

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COVID-19 (Caruso et al., 2023), raising the hypothesis of the presence of protective genes and/or variants.

This unique subset of individuals demonstrated remarkable resilience by passing or recovering from COVID-19 without complications and before the advent of vaccination. The SARS-CoV-2 infection is just one example of resilience among the elderly. Despite their advanced age, there are remarkable other cases of healthy and active centenarians who, amidst various environmental adversities, remain robust and do not succumb to them (Borras et al., 2020). Therefore, studying these long-lived individuals provides a rare opportunity to explore the genetic and biological factors contributing to longevity and disease resilience.

Aging is a complex process influenced by genetic, environmental, and lifestyle factors (Dziechciaż and Filip, n.d.; Costa et al., 2019; Stern et al., 2023). Despite significant progress in understanding the biology of aging, the genetic determinants that allow certain individuals to achieve extreme longevity remain elusive. A powerful tool that could help elucidate these determinants is whole-exome sequencing (WES), which allows for the comprehensive analysis of the protein-coding regions of the genome (Yang et al., 2014; van den Akker et al., 2015). By focusing on these regions, WES can identify genetic variants that may contribute to longevity and resilience, offering valuable insights into the biology of aging and the potential for developing targeted interventions to promote healthy aging. Additionally, WES can identify pathogenic variants that predispose individuals to various diseases, including cancer and cardiovascular conditions. The American College of Medical Genetics and Genomics (ACMG) has established guidelines for reporting incidental findings of pathogenic variants in 59 genes, even if unrelated to the individual's current clinical presentation (Miller et al., 2022).

In this study, we performed WES on a cohort of 100 Brazilian nonagenarians and centenarians who recovered from COVID-19 before the onset of the Brazilian COVID-19 vaccination program. Among the participants were three unvaccinated supercentenarians, who were reported by national media to be the longest-lived individuals in South America to have recovered from COVID-19 (de Castro et al., 2022). Our aim was to identify any pathogenic variants and evaluate their potential impact on longevity and disease resilience. The discovery of such variants in these individuals, who have surpassed 90 years of age and successfully recovered from a life-threatening viral infection, raises intriguing questions about the presence of protective genetic factors. Understanding these factors could have significant implications for clinical practice and the broader field of genetics.

2. Methods

2.1. Volunteer recruitment, blood collection, and sample processing

A cohort of 100 Brazilian nonagenarians and centenarians who recovered from COVID-19 was recruited for blood collection at least 60 days post-infection. For DNA extraction and plasma isolation, samples were collected in vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) (BD Biosciences, USA, Catalog #360057) following established protocols at our Research Center. The samples were obtained between June and October 2020, prior to the emergence of new SARS-CoV-2 variants in Brazil (notably the Gamma variant) and before the initiation of the Brazilian COVID-19 vaccination program. Serological assays confirmed SARS-CoV-2 infection in all individuals. Baseline characteristics of these long-lived individuals, who are carriers of pathogenic variants, are detailed in Table 1. The severity of COVID-19 was classified according to the clinical spectrum outlined in the World Health Organization's updated guidelines for COVID-19 treatment (Gandhi et al., 2020). The study flowchart detailing the recruitment process, sample collection, and analyses is presented in Supplementary Figure 1.

2.2. Whole-exome sequencing

Whole-exome sequencing was performed using the NovaSeq 6000 system (Illumina, USA) with a 150-base paired-end dual-index read format. For library preparation, the Nextera Rapid Capture Custom Enrichment Kit or Nextera Flex Kit (Illumina, USA) and the IDT xGen-V1 capture kit were used, following the manufacturer's protocols. Reads were aligned to the human reference genome GRCh38 using the Burrow-Wheeler Aligner 0.7.15 (BWA) (https://github.com/lh3/bwa/tree/master/bwakit). Post-alignment, Picard 2.18.7 (https://broadinstitute.github.io/picard) was employed to mark duplicates, and GATK 4.0.9 was used to perform Base Quality Score Recalibration (BQSR) with the BaseRecalibrator tool, ultimately generating individual GVCFs.

2.3. Evaluation of genetic susceptibility to severe COVID-19

To investigate potential genetic susceptibility to severe COVID-19 in our cohort of 100 Brazilian nonagenarians and centenarians who recovered from COVID-19, we evaluated specific genes associated with monogenic inborn errors of immunity. This approach is aligned with the objectives of the COVID Human Genetic Effort (https://www.covidhge.com), which hypothesizes that life-threatening COVID-19 may result from such genetic errors (Q. Zhang et al. 2020). We focused on genes implicated in type I interferon (IFN) immunity, particularly those previously linked to severe viral infections, including influenza. Specifically, we sequenced the exomes of our participants to examine three core genes (*TLR3, IRF7*, and *IRF9*) known to be mutated in patients with life-threatening influenza. Additionally, we analyzed twelve other genes (*IFIH1, IFNAR1, IFNAR2, IRAK4, MYD88, STAT1, STAT2, TBK1, TICAM1, TLR7, TYK2 and UNC93B1*) involved in the TLR3-dependent type I IFN induction pathway and the *IRF7*- and *IRF9*-dependent type I IFN amplification pathway. Main filters used: allelic frequency on gnomAD v3.1 below or equal to 1 %, CADD phred score equal or above 20. Different modes of inheritance at these 15 loci were considered to identify potential primary immunodeficiencies that may contribute to the susceptibility to severe COVID-19.

2.4. Secondary findings

The American College of Medical Genetics and Genomics (ACMG) has provided guidance for reporting secondary findings in clinical exome and genome sequencing (ES/GS) since 2013. In this study, we analyzed all genes listed in the v3.1 guidance, released in 2022 (Miller et al. 2022). All variants identified in these genes were evaluated, and potential candidates were selected based on specific criteria, including population allele frequency, variant type, ClinVar classification, and other factors. These candidate variants were then manually evaluated

Table 1
Demographic and clinical data of the participants.

ID	01	02	03	04	05	06
Sex	F	M	F	F	F	M
Age	97	96	104	90	93	110
Comorbidities	Hypertension	–	Hypertension Vision and Hearing Losses	Hypertension COPD Heart Failure	Hypertension	Hypertension
Disease severity	Moderate	Asymptomatic	Moderate	Severe	Mild	Moderate

and classified according to international guidelines (ACMG /ClinGen). The ACMG/ClinGen classification system provides a standardized approach for interpreting the clinical significance of genetic variants. This system categorizes variants into five classes based on criteria such as population data, computational and predictive data, functional data, segregation data, and de novo data. By combining these different types of evidence, the system offers a comprehensive assessment that facilitates accurate and consistent variant classification in clinical genetic testing. The five classes are: Pathogenic, Likely Pathogenic, Uncertain Significance (VUS), Likely Benign and Benign.

3. Results

3.1. Monogenic inborn errors of immunity

We have filtered variants across 15 genes associated with immunodeficiencies in nonagenarians and centenarians and respective flanking regions. Considering the nature of the cohort (survival/full recovery from COVID-19), the variants found in these genes are likely to be benign, even considering its potential deleteriousness inferred by CADD. Comparing our cohort with two bigger ones with available data of WGS: the cohort from the genoMAd database and the census-based cohort SABE1171/ABraOM of elderly Brazilian individuals, previously obtained by our group (Naslavsky et al. 2022), we find two homozygous individuals for rare variants in *TYK2* might provide insights into the inflammatory response of these elderly, to be confirmed in further studies (Tables 2 and 3).

3.2. Identification of ACMG-Listed genetic variants in COVID-19 survivors

Among the cohort of long-lived individuals, four participants (4/100) were identified as carriers of variants in genes recommended for reporting by the American College of Medical Genetics and Genomics (ACMG). The identified variants were classified according to the ACMG/ClinGen guidelines, which encompass a range of criteria including population allele frequency, computational and predictive data, functional studies, and segregation data. Table 4 provides a detailed summary of the individual IDs, the specific genes involved and the nature of the genetic variants.

4. Discussion

Identifying pathogenic variants in our cohort of nonagenarians and centenarians, who have successfully recovered from COVID-19, offers intriguing insights into the genetics of longevity and disease resilience. Despite carrying pathogenic variants associated with serious conditions such as cancer predisposition and cardiovascular diseases, these individuals have surpassed 90 years of age and withstood a life-threatening viral infection. This suggests the presence of genetic protective factors that may counterbalance the deleterious effects of these pathogenic variants. These protective factors may enhance immune function, mitigate chronic inflammation, or promote cellular repair mechanisms, contributing to their exceptional longevity and resilience. Further research is needed to identify and understand these protective genetic elements, which could have significant implications for developing strategies to enhance healthspan and longevity in the general population. Additionally, the interplay between genetic background and age-associated epigenetic changes plays a crucial role in determining which genes and molecular pathways are expressed, impacting both longevity and susceptibility to infections (J. Zhang, Wang, and Liu 2023; Costa et al., 2019; Crimi et al. 2020).

Biological aging is marked by critical epigenetic changes, including DNA methylation, histone modifications, and disruptions in protein homeostasis, all of which influence the expression of genes involved in aging and immune function (Zhang et al., 2023). These epigenetic alterations, coupled with genetic background, create variability in aging outcomes and susceptibility to diseases, particularly in response to infections like severe respiratory viruses. Notably, viruses such as SARS-CoV-2 and influenza exploit these epigenetic mechanisms to disrupt host immune responses, exacerbate inflammation, and worsen overall disease outcomes. For example, MERS-CoV and H5N1 have been shown to modulate immune responses through DNA methylation and histone modifications, mechanisms likely relevant in the context of COVID-19 (Crimi et al. 2020). Interestingly, centenarians exhibit distinct epigenetic signatures, such as reduced DNA methylation, which may offer protective effects and contribute to their remarkable resilience to age-related diseases and infections (Costa et al., 2019). By unraveling the complex interplay between genetic and epigenetic factors, researchers can unlock new therapeutic strategies aimed at targeting epigenetic pathways to promote healthier aging and strengthen immune defenses, particularly in vulnerable elderly populations.

Our analysis has identified some genes (*TYK2, RYR1, DSP, BRCA1, BRCA2, and TTN*) harboring potentially deleterious variants in our cohort of nonagenarians and centenarians who have successfully recovered from COVID-19. The *TYK2* gene encodes tyrosine kinase 2, a member of the Janus kinase family, playing a pivotal role in the signal transduction pathways of various cytokines critical for immune response regulation and inflammation. The *RYR1* gene encodes the ryanodine receptor 1, a protein forming channels responsible for releasing calcium ions from intracellular stores, essential for skeletal muscle function. The *DSP* gene encodes desmoplakin, a protein predominantly found in cardiac and skin cells, which is a major component of desmosomes providing cellular adhesion, structural integrity, and involvement in signaling pathways, differentiation, and apoptosis. The *BRCA1/BRCA2* genes encode tumor suppressor proteins playing a critical role in maintaining genomic stability by repairing damaged DNA and preventing uncontrolled cellular proliferation. The *TTN* gene encodes titin, a large protein integral to the structure and function of both skeletal and cardiac muscles, with various isoforms produced in different muscle types, and within muscle cells, titin is a crucial component of sarcomeres.

Moreover, our study underscores the importance of considering the broader context of genetic findings in long-lived individuals. The ACMG's guidelines for reporting incidental findings are crucial for clinical practice, providing actionable information for disease

Table 2
Variants exclusive to nonagenarians and centenarians (absent in a census-based cohort of Brazilian elderly − SABE1171/ABraOM).

Gene	Genomic coordinate (hg38)						Allele counts (AC)		
	Chr	Pos	Ref	Alt	Transcript	Consequence	gnomAD v3.1 (AN ~ 151 k)	SABE1171 (AN = 2342)	This sample (AN = 198)
IFIH1	chr2	162,288,247	C	T	NM_022168	p.C328Y	0	0	1
MYD88	chr3	38,141,218	G	A	NM_002468:	p.D275N	0	0	1
IRAK4	chr12	43,771,251	A	G	INM_016123	p.S65G	0	0	1
TYK2	chr19	10,353,559	T	C	NM_022168	p.Q999R	0	0	1
	chr19	10,354,563	G	T	NM_022168	p.D888E	5	0	1
	chr19	10,357,799	C	T	NM_022168	p.G811R	1	0	1
	chr19	10,365,515	A	C	NM_022168	p.C328Y	7	0	1

Table 3
Variants overrepresented in nonagenarians and centenarians (compared with a census-based cohort of Brazilian elderly – SABE1171/ABraOM).

Gene	Genomic coordinate (hg38)						Allele counts (AC)			
	Chr	Pos	Ref	Alt	Transcript	Consequence	gnomAD v3.1 (AN ~ 151 k)	SABE1171 (AN = 2342)	This sample (AN = 198)	
IFIH1	chr2	162268109	C	T	NM_022168	p.V929I	291 (1 homozygote)	4 (all heterozygotes)	1 heterozygote	**Voluntary ID**
TYK2	chr19	10350910	T	C	NM_002468	p.E1163G	490 (4 homozygotes)	7 (all heterozygotes)	1homozygote	**01**
	chr19	10,378,250	C	T	INM_016123	p.A53T	1100 (8 homozygotes)	9 (all heterozygotes)	1 homozygote	**02**

Table 4
ACMG-Listed Genetic Variants in Long-Lived COVID-19 Survivors.

ID	Gene	Transcript	c.	p.	Classification
03	*RYR1*	NM_000540.3	0c.8026C > T	p.(Arg2676Trp)	Likely Pathogenic
04	*DSP*	NM_004415.4	0c.5800C > T	p.(Arg1934*)	Likely Pathogenic
	BRCA2	NM_000059.4	0c.8488-1G > A	p.(?)	Pathogenic
05	*BRCA1*	NM_007294.4	0c.470_471del	p.(Ser157*)	Pathogenic
06	*TTN*	NM_001267550.2	0c.14635C > T	p.(Gln4879*)	Likely Pathogenic

prevention and management. However, our findings highlight the complexity of interpreting these variants in the context of aging and resilience. The presence of pathogenic variants in long-lived individuals raises questions about the interplay between genetic risk factors and protective mechanisms. It also emphasizes the need for a nuanced approach to genetic counseling and the potential benefits of personalized healthcare strategies that consider an individual's unique genetic makeup and life history. As we continue to explore the genetic determinants of longevity, integrating genomic data with clinical and environmental factors will be essential for advancing our understanding of healthy aging and improving health outcomes for older adults.

5. Conclusion

Our findings highlight the resilience and potential genetic protective factors in long-lived individuals who recovered from COVID-19, despite carrying pathogenic variants. This underscores the complexity of genetic contributions to disease resilience and longevity and the need for further research.

CRediT authorship contribution statement

Mateus V. de Castro: Writing – review & editing, Writing – original draft, Methodology, Investigation; Conceptualization. **Cristina Sábato:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Raíssa M. Dandalo-Girardi:** Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Monize V.R. Silva:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Luiz P. Dell'Aquila:** Data curation. **Álvaro Razuk-Filho:** Data curation. **Pedro B. Batista-Júnior:** Data curation. **Michel S. Naslavsky:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis. **Mayana Zatz:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization..

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2024.149025.

Data availability

Data will be made available on request.

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