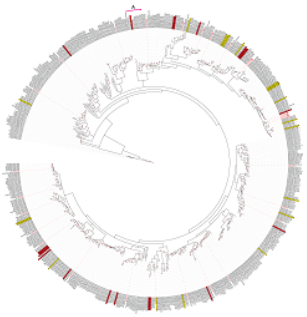

Update of the keratin gene family: evolution, tissue-specific expression patterns, and relevance to clinical disorders

Keratin genes comprise the largest subset of intermediate filament genes, which arose during early metazoan evolution to provide mechanical support for plasma membranes in contact with other cells and the extracellular matrix. During evolution, these keratin genes rapidly multiplied and diversified in lungfish and amphibian genomes, concomitant with the sea-to-land-animal divergence (440 to 410 million years ago). The human genome has 27 of 28 type I "acidic" keratin genes clustered at chromosome 17q21.2, and all 26 type II "basic" keratin genes clustered at chromosome 12q13.13. These two clusters ("evolutionary blooms") of type I and type II keratin genes, each located along a chromosomal segment, have been found in all land-animal vertebrate genomes examined, but not fishes.
To further understand the role of keratins in human disease, Ho et al. (2022) performed an extensive analysis of the evolutionary relationship of paralogous intermediate filaments within humans and representative model organisms; they screened 259 species and subspecies in 20 phyla of animals, from sponge to human. They then performed a phylogenetically-directed, Bayesian comparative genomic assay of the history of type I and type II keratins across the Tree-of-Life. Finally, the authors contextualize the expression and interaction of keratins to provide insight into the impact of keratin on human health. In the current ClinVar database, they found 26 human disease-causing variants within the various domains of keratin proteins.

Articles

Why are keratins important?

Jeffrey Nicholas Fisk and Daniel W. Nebert

Editorial | 30 January 2022

The Gene family update to this article has been published in *Human Genomics* 2022 **16**:1

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Updates from the HUGO Gene Nomenclature Committee (HGNC) relevant to *Human Genomics* readers.

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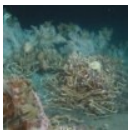
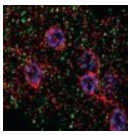


Genomic study of tubeworms reveals clues on how species adapt to extreme deep-sea environments

19 November 2019

Village dog DNA reveals genetic changes caused by domestication

28 June 2018



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07 March 2018

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Correction to: Whole exome sequencing identifies novel candidate genes that modify chronic obstructive pulmonary disease susceptibility

Shannon Bruse, Michael Moreau, Yana Bromberg, Jun-Ho Jang, Nan Wang, Hongseok Ha, Maria Picchi, Yong Lin, Raymond J. Langley, Clifford Qualls, Julia Klesney-Tait, Joseph Zabner, Shuguang Leng, Jenny Mao, Steven A. Belinsky, Jinchuan Xing...

Human Genomics 2021 15:74
Correction | Published on: 30 December 2021

The original article was published in *Human Genomics* 2016 **10**:1

Full Text PDF

Identification of a novel signature based on unfolded protein response-related gene for predicting prognosis in bladder cancer

The unfolded protein response (UPR) served as a vital role in the progression of tumors, but the molecule mechanisms of UPR in bladder cancer (BLCA) have been not fully investigated.

Ke Zhu, Liu Xiaoqiang, Wen Deng, Gongxian Wang and Bin Fu

Human Genomics 2021 15:73
Primary research | Published on: 20 December 2021

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Detection of low-level parental somatic mosaicism for clinically relevant SNVs and indels identified in a large exome sequencing dataset

Due to the limitations of the current routine diagnostic methods, low-level somatic mosaicism with variant allele fraction (VAF) < 10% is often undetected in clinical settings. To date, only a few studies have...

Daniel D. Domogala, Tomasz Gambin, Roni Zemet, Chung Wah Wu, Katharina V. Schulze, Yaping Yang, Theresa A. Wilson, Ido Machol, Pengfei Liu and Paweł Stankiewicz

Human Genomics 2021 15:72
Primary research | Published on: 20 December 2021

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Driving mosaicism: somatic variants in reference population databases and effect on variant interpretation in rare genetic disease

Genetic variation databases provide invaluable information on the presence and frequency of genetic variants in the 'untargeted' human population, aggregated with the primary goal to facilitate the interpretat...

Vladimir Avramović, Simona Denise Frederiksen, Marjana Brkić and Maja Tarailo-Graovac

Human Genomics 2021 15:71
Primary research | Published on: 14 December 2021

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Estimating prevalence of human traits among populations from polygenic risk scores

The genetic basis of phenotypic variation across populations has not been well explained for most traits. Several factors may cause disparities, from variation in environments to divergent population genetic s...

Britney E. Graham, Brian Plotkin, Louis Muglia, Jason H. Moore and Scott M. Williams

Human Genomics 2021 15:70
Primary research | Published on: 13 December 2021

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A regulatory miRNA–mRNA network is associated with transplantation response in acute kidney injury

Acute kidney injury (AKI) is a life-threatening complication characterized by rapid decline in renal function, which frequently occurs after transplantation surgery. However, the molecular mechanism underlying...

Duan Guo, Yu Fan, Ji-Rong Yue and Tao Lin

Human Genomics 2021 15:69
Primary research | Published on: 9 December 2021

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Single-cell transcriptome identifies molecular subtype of autism spectrum disorder impacted by de novo loss-of-function variants regulating glial cells

In recent years, several hundred autism spectrum disorder (ASD) implicated genes have been discovered impacting a wide range of molecular pathways. However, the molecular underpinning of ASD, particularly from...

Nasna Nassir, Asma Bankapur, Bisan Samara, Abdulrahman Ali, Awab Ahmed, Ibrahim M. Inuwa, Mehdi Zarrei, Seyed Ali Safizadeh Shabestari, Ammar AlBanna, Jennifer L. Howe, Bakhrom K. Berdiev, Stephen W. Scherer, Marc Woodbury-Smith and Mohammed Uddin

Human Genomics 2021 15:68
Primary research | Published on: 21 November 2021

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RNA-seq driven expression and enrichment analysis to investigate CVD genes with associated phenotypes among high-risk heart failure patients

Heart failure (HF) is one of the most common complications of cardiovascular diseases (CVDs) and among the leading causes of death in the US. Many other CVDs can lead to increased mortality as well. Investigat...

Zeeshan Ahmed, Saman Zeeshan and Bruce T. Liang

Human Genomics 2021 15:67
Primary research | Published on: 13 November 2021

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A robust and stable gene selection algorithm based on graph theory and machine learning

Nowadays we are observing an explosion of gene expression data with phenotypes. It enables us to accurately identify genes responsible for certain medical condition as well as classify them for drug target. Li...

Subrata Saha, Ahmed Soliman and Sanguthevar Rajasekaran

Human Genomics 2021 15:66
Primary research | Published on: 9 November 2021

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Breast cancer in West Africa: molecular analysis of *BRCA* genes in early-onset breast cancer patients in Burkina Faso

Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among women in Africa after cervical cancer. Even if the epidemiological data are now aligned with...

Michela Biancolella, Nabonswindé Lamoussa Marie Ouédraogo, Nayi Zongo, Théodora Mahoukèdè Zohoncon, Barbara Testa, Barbara Rizzacasa, Andrea Latini, Chiara Conte, Tégwindé Rebeca Compaore, Charlemagne Marie Rayang-Newendé Ouedraogo, Si Simon Traore, Jacques Simpore and Giuseppe Novelli

Human Genomics 2021 15:65
Primary research | Published on: 30 October 2021

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Genetic polymorphisms of Vascular Endothelial Growth Factor (VEGF) associated with endometriosis in Nigerian women

To determine if genetic polymorphism of VEGF is associated with the development of endometriosis in Nigerian women.

Ochuwa Adiketu Babah, Oyesola Oyewole Ojewunmi, Akinniyi Adediran Osuntoki, Melissa A. Simon and Bosede Bukola Afolabi

Human Genomics 2021 15:64
Primary research | Published on: 30 October 2021

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Phenotypic intrafamilial variability including H syndrome and Rosai–Dorfman disease associated with the same c.1088G > A mutation in the *SLC29A3* gene

Mutations in the *SLC29A3* gene, which encodes the nucleoside transporter hENT3, have been implicated in syndromic forms of histiocytosis including H syndrome, pigmented hypertrichosis with insulin-dependent diabet...

Hamza Chouk, Mohamed Ben Rejeb, Lobna Boussofara, Haïfa Elmabrouk, Najet Ghariani, Badreddine Sriha, Ali Saad, Dorra H'Mida and Mohamed Denguezli

Human Genomics 2021 15:63
Primary research | Published on: 17 October 2021

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Development of the pharmacogenomics and genomics literacy framework for pharmacists

Pharmacists play a unique role in integrating genomic medicine and pharmacogenomics into the clinical practice and to translate pharmacogenomics from bench to bedside. However, the literature suggests that the...

Azhar T. Rahma, Iffat Elbarazi, Bassam R. Ali, George P. Patrinos, Luai A. Ahmed, Mahanna Elsheik and Fatma Al-Maskari

Human Genomics 2021 15:62
Primary research | Published on: 16 October 2021

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Seven novel glucose-6-phosphate dehydrogenase (G6PD) deficiency variants identified in the Qatari population

Glucose-6-phosphate dehydrogenase deficiency (G6PDD) is the most common red cell enzymopathy in the world. In Qatar, the incidence of G6PDD is estimated at around 5%; however, no study has investigated the gen...

Shaza Malik, Roan Zaied, Najeeb Syed, Puthen Jithesh and Mashael Al-Shafai

Human Genomics 2021 15:61
Primary research | Published on: 7 October 2021

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Protective chromosome 1q32 haplotypes mitigate risk for age-related macular degeneration associated with the *CFH-CFHR5* and *ARMS2/HTRA1* loci

Single-variant associations with age-related macular degeneration (AMD), one of the most prevalent causes of irreversible vision loss worldwide, have been studied extensively. However, because of a lack of ref...

Chris M. Pappas, Moussa A. Zouache, Stacie Matthews, Caitlin D. Faust, Jill L. Hageman, Brandi L. Williams, Burt T. Richards and Gregory S. Hageman

Human Genomics 2021 15:60
Primary research | Published on: 25 September 2021

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Correction to: Update on human genetic susceptibility to COVID-19: susceptibility to virus and response

Vito Luigi Colona, Vasilis Vasiliou, Jessica Watt, Giuseppe Novelli and Juergen K. V. Reichardt

Human Genomics 2021 15:59
Correction | Published on: 18 September 2021

The original article was published in *Human Genomics* 2021 **15**:57

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Evaluation of low-pass genome sequencing in polygenic risk score calculation for Parkinson's disease

Low-pass sequencing (LPS) has been extensively investigated for applicability to various genetic studies due to its advantages over genotype array data including cost-effectiveness. Predicting the risk of comp...

Sungjae Kim, Jong-Yeon Shin, Nak-Jung Kwon, Chang-Uk Kim, Changhoon Kim, Chong Sik Lee and Jeong-Sun Seo

Human Genomics 2021 15:58
Primary research | Published on: 28 August 2021

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Update on human genetic susceptibility to COVID-19: susceptibility to virus and response

Vito Luigi Colona, Vasilis Vasiliou, Jessica Watt, Giuseppe Novelli and Juergen K. V. Reichardt

Human Genomics 2021 15:57
Editorial | Published on: 25 August 2021

The Correction to this article has been published in *Human Genomics* 2021 **15**:59

The Review to this article has been published in *Human Genomics* 2021 **15**:27

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Correction to: The evolutionary genetics of lactase persistence in seven ethnic groups across the Iranian plateau

Hadi Charati, Min-Sheng Peng, Wei Chen, Xing-Yan Yang, Roghayeh Jabbari Ori, Mohsen Aghajanpour-Mir, Ali Esmailizadeh and Ya-Ping Zhang

Human Genomics 2021 15:56
Correction | Published on: 24 August 2021

The original article was published in *Human Genomics* 2019 **13**:7

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Abnormal expression profile of plasma-derived exosomal microRNAs in patients with treatment-resistant depression

Whether microRNAs (miRNAs) from plasma exosomes might be dysregulated in patients with depression, especially treatment-resistant depression (TRD), remains unclear, based on study of which novel biomarkers and...

Lian-Di Li, Muhammad Naveed, Zi-Wei Du, Huachen Ding, Kai Gu, Lu-Lu Wei, Ya-Ping Zhou, Fan Meng, Chun Wang, Feng Han, Qi-Gang Zhou and Jing Zhang

Human Genomics 2021 15:55
Primary research | Published on: 21 August 2021

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Perception of personalized medicine, pharmacogenomics, and genetic testing among undergraduates in Hong Kong

The global development and advancement of genomic medicine in the recent decade has accelerated the implementation of personalized medicine (PM) and pharmacogenomics (PGx) into clinical practice, while catalyz...

Nicholas Yan Chai Cheung, Jasmine Lee Fong Fung, Yvette Nga Chung Ng, Wilfred Hing Sang Wong, Claudia Ching Yan Chung, Christopher Chun Yu Mak and Brian Hon Yin Chung

Human Genomics 2021 15:54
Primary research | Published on: 18 August 2021

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Identification of subgroups along the glycolysis-cholesterol synthesis axis and the development of an associated prognostic risk model

Skin cutaneous melanoma (SKCM) is one of the most highly prevalent and complicated malignancies. Glycolysis and cholesterogenesis pathways both play important roles in cancer metabolic adaptations. The main ai...

Enchong Zhang, Yijing Chen, Shurui Bao, Xueying Hou, Jing Hu, Oscar Yong Nan Mu, Yongsheng Song and Liping Shan

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Established and candidate transthyretin amyloidosis variants identified in the Saudi population by data mining

Familial transthyretin (TTR) amyloidosis (ATTR) is an autosomal dominant disease with significant phenotypic heterogeneity. Its prevalence in Saudi Arabia has not previously been investigated. An existing exom...

Mohamed Abouelhoda, Dania Mohty, Islam Alayary, Brian F. Meyer, Stefan T. Arold, Bahaa M. Fadel and Dorota Monies

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Primary research | Published on: 11 August 2021

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A novel machine learning-based approach for the computational functional assessment of pharmacogenomic variants

The field of pharmacogenomics focuses on the way a person's genome affects his or her response to a certain dose of a specified medication. The main aim is to utilize this information to guide and personalize ...

Maria-Theodora Pandi, Maria Koromina, Iordanis Tsafaridis, Sotirios Patsilinakos, Evangelos Christoforou, Peter J. van der Spek and George P. Patrinos

Human Genomics 2021 15:51
Primary research | Published on: 9 August 2021

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LncRNA-TUG1 promotes the progression of infantile hemangioma by regulating miR-137/IGFBP5 axis

Previous studies indicated that lncRNA taurine upregulated gene 1 (TUG1) played essential roles in human cancers. This study aimed to investigate its function in infantile hemangioma (IH).

Lili Zhou, Xiao Jia and Xiangzheng Yang

Human Genomics 2021 15:50
Primary research | Published on: 6 August 2021

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The limits of clinical findings in similar phenotypes, from Carpenter to ATRX syndrome using a whole exome sequencing approach: a case review

The diagnostic process for uncommon disorders with similar manifestations is complicated and requires newer technology, like gene sequencing for a correct diagnosis.

Samantha S. Sáenz, Benjamin Arias, Kazuyoshi Hosomichi and Vanessa I. Romero

Human Genomics 2021 15:49
Review | Published on: 4 August 2021

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A comprehensive analysis of copy number variation in a Turkish dementia cohort

Copy number variants (CNVs) include deletions or multiplications spanning genomic regions. These regions vary in size and may span genes known to play a role in human diseases. As examples, duplications and tr...

Nadia Dehghani, Gamze Guven, Celia Kun-Rodrigues, Catarina Gouveia, Kalina Foster, Hasmet Hanagasi, Ebba Lohmann, Bedia Samanci, Hakan Gurvit, Basar Bilgic, Jose Bras and Rita Guerreiro

Human Genomics 2021 15:48
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Altered splicing associated with the pathology of inflammatory bowel disease

Aberrant splicing of individual genes is a well-known mechanism promoting pathology for a wide range of conditions, but disease is less commonly attributed to global disruption of exon usage. To explore the po...

Kiera Berger, Hari Somineni, Jarod Prince, Subra Kugathasan and Greg Gibson

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Implementation and implications for polygenic risk scores in healthcare

Increasing amounts of genetic data have led to the development of polygenic risk scores (PRSs) for a variety of diseases. These scores, built from the summary statistics of genome-wide association studies (GWA...

John L. Slunecka, Matthijs D. van der Zee, Jeffrey J. Beck, Brandon N. Johnson, Casey T. Finnicum, René Pool, Jouke-Jan Hottenga, Eco J. C. de Geus and Erik A. Ehli

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Review | Published on: 20 July 2021

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ACER3-related leukoencephalopathy: expanding the clinical and imaging findings spectrum due to novel variants

Leukodystrophies are the main subgroup of inherited CNS white matter disorders which cause significant mortality and morbidity in early years of life. Diagnosis is mostly based on clinical context and neuroima...

Ali Zare Dehnavi, Erfan Heidari, Maryam Rasulinezhad, Morteza Heidari, Mahmoud Reza Ashrafi, Mohammad Mahdi Hosseini, Fatemeh Sadeghzadeh, Mohammad-Sadegh Fallah, Noushin Rostampour, Amir Bahraini, Masoud Garshasbi and Ali Reza Tavasoli

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Coding and noncoding variants in *EBF3* are involved in HADDS and simplex autism

Previous research in autism and other neurodevelopmental disorders (NDDs) has indicated an important contribution of protein-coding (coding) de novo variants (DNVs) within specific genes. The role of de novo n...

Evin M. Padhi, Tristan J. Hayeck, Zhang Cheng, Sumantra Chatterjee, Brandon J. Mannion, Marta Byrska-Bishop, Marjolaine Willems, Lucile Pinson, Sylvia Redon, Caroline Benech, Kevin Uguen, Séverine Audebert-Bellanger, Cédric Le Marechal, Claude Férec, Stephanie Efthymiou, Fatima Rahman...

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High-throughput screening of circRNAs reveals novel mechanisms of tuberous sclerosis complex-related renal angiomyolipoma

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disease characterized by lesions throughout the body. Our previous study showed the abnormal up-regulation of miRNAs plays an important part in the...

Yang Zhao, Hao Guo, Wenda Wang, Guoyang Zheng, Zhan Wang, Xu Wang and Yushi Zhang

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TMEM263: a novel candidate gene implicated in human autosomal recessive severe lethal skeletal dysplasia

Skeletal dysplasia is a common, clinically and genetically heterogeneous disorder in the human population. An increasing number of different genes are being identified causing this disorder. We used whole exom...

Mahsa Sadat Asl Mohajeri, Atieh Eslahi, Zeinab Khazaii, Mohammad Reza Moradi, Reza Pazhoomand, Shima Farrokhi, Masoumeh Heidari Feizabadi, Farzaneh Alizadeh and Majid Mojarrad

Human Genomics 2021 15:42
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Performances of NIPT for copy number variations at different sequencing depths using the semiconductor sequencing platform

To evaluate the performance of noninvasive prenatal testing (NIPT) and NIPT-PLUS for the detection of genome-wide microdeletion and microduplication syndromes (MMSs) at different sequencing depths. The NIPT se...

Jiexia Yang, Jing Wu, Haishan Peng, Yaping Hou, Fangfang Guo, Dongmei Wang, Haoxin Ouyang, Yixia Wang and Aihua Yin

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Single-cell chromatin accessibility landscape of human umbilical cord blood in trisomy 18 syndrome

Trisomy 18 syndrome (Edwards syndrome, ES) is a type of aneuploidy caused by the presence of an extra chromosome 18. Aneuploidy is the leading cause of early pregnancy loss, intellectual disability, and multip...

Xiaofen Qiu, Haiyan Yu, Hongwei Wu, Zhiyang Hu, Jun Zhou, Hua Lin, Wen Xue, Wanxia Cai, Jiejing Chen, Qiang Yan, Weier Dai, Ming Yang, Donge Tang and Yong Dai

Human Genomics 2021 15:40
Primary research | Published on: 30 June 2021

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Identification of hub genes associated with prognosis, diagnosis, immune infiltration and therapeutic drug in liver cancer by integrated analysis

Liver cancer is one of the most common cancers and causes of cancer death worldwide**.** The objective was to elucidate novel hub genes which were benefit for diagnosis, prognosis, and targeted therapy in liver cance...

Xinyi Lei, Miao Zhang, Bingsheng Guan, Qiang Chen, Zhiyong Dong and Cunchuan Wang

Human Genomics 2021 15:39
Primary research | Published on: 29 June 2021

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HCP5, as the sponge of miR-1291, facilitates AML cell proliferation and restrains apoptosis via increasing PIK3R5 expression

Acute myeloid leukemia (AML) is recognized as a hematological neoplasm with heterogenetic cytology and short-term outcome. HCP5 has been proven to be related with the pathogenesis of AML. However, the underlyi...

Yan Liu, Xue-Bing Jing, Zhen-Cheng Wang and Qing-Kun Han

Human Genomics 2021 15:38
Primary research | Published on: 29 June 2021

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Advancing clinical genomics and precision medicine with GVViZ: FAIR bioinformatics platform for variable gene-disease annotation, visualization, and expression analysis

Genetic disposition is considered critical for identifying subjects at high risk for disease development. Investigating disease-causing and high and low expressed genes can support finding the root causes of u...

Zeeshan Ahmed, Eduard Gibert Renart, Saman Zeeshan and XinQi Dong

Human Genomics 2021 15:37
Primary research | Published on: 26 June 2021

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Regulatory *VCAN* polymorphism is associated with shoulder pain and disability in breast cancer survivors

Shoulder morbidity following breast cancer treatment is multifactorial. Despite several treatment- and patient-related factors being implicated, unexplained inter-individual variability exists in the developme...

Trevor S. Mafu, Alison V. September and Delva Shamley

Human Genomics 2021 15:36

Primary research | Published on: 23 June 2021

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Correction to: Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities

Tesfaye B. Mersha and Tilahun Abebe

Human Genomics 2021 15:35
Correction | Published on: 15 June 2021

The original article was published in *Human Genomics* 2015 **9**:1

› Full Text › PDF

Mitochondrial genome copy number measured by DNA sequencing in human blood is strongly associated with metabolic traits via cell-type composition differences

Mitochondrial genome copy number (MT-CN) varies among humans and across tissues and is highly heritable, but its causes and consequences are not well understood. When measured by bulk DNA sequencing in blood, ...

Liron Ganel, Lei Chen, Ryan Christ, Jagadish Vangipurapu, Erica Young, Indraniel Das, Krishna Kanchi, David Larson, Allison Regier, Haley Abel, Chul Joo Kang, Alexandra Scott, Aki Havulinna, Charleston W. K. Chiang, Susan Service, Nelson Freimer...

Human Genomics 2021 15:34
Primary research | Published on: 7 June 2021

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Predicting anticancer hyperfoods with graph convolutional networks

Recent efforts in the field of nutritional science have allowed the discovery of disease-beating molecules within foods based on the commonality of bioactive food molecules to FDA-approved drugs. The pioneerin...

Guadalupe Gonzalez, Shunwang Gong, Ivan Laponogov, Michael Bronstein and Kirill Veselkov

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Correction to: An application of slow feature analysis to the genetic sequences of coronaviruses and influenza viruses

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An application of slow feature analysis to the genetic sequences of coronaviruses and influenza viruses

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Wulandari et al. Human Genomics (2021) 15:29
https://doi.org/10.1186/s40246-021-00330-7

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Initial study on TMPRSS2 p.Val160Met genetic variant in COVID-19 patients

Laksmi Wulandari[1†], Berliana Hamidah[2†], Cennikon Pakpahan[2,3†], Nevy Shinta Damayanti[4], Neneng Dewi Kurniati[5], Christophorus Oetama Adiatmaja[6,7], Monica Rizky Wigianita[6], Soedarsono[1], Dominicus Husada[8], Damayanti Tinduh[9], Cita Rosita Sigit Prakoeswa[10], Anang Endaryanto[8], Ni Nyoman Tri Puspaningsih[11,12], Yasuko Mori[13], Maria Inge Lusida[14,15], Kazufumi Shimizu[13,16] and Delvac Oceandy[17*]

Abstract

Background: Coronavirus disease 2019 (COVID-19) is a global health problem that causes millions of deaths worldwide. The clinical manifestation of COVID-19 widely varies from asymptomatic infection to severe pneumonia and systemic inflammatory disease. It is thought that host genetic variability may affect the host's response to the virus infection and thus cause severity of the disease. The SARS-CoV-2 virus requires interaction with its receptor complex in the host cells before infection. The transmembrane protease serine 2 (TMPRSS2) has been identified as one of the key molecules involved in SARS-CoV-2 virus receptor binding and cell invasion. Therefore, in this study, we investigated the correlation between a genetic variant within the human *TMPRSS2* gene and COVID-19 severity and viral load.

Results: We genotyped 95 patients with COVID-19 hospitalised in Dr Soetomo General Hospital and Indrapura Field Hospital (Surabaya, Indonesia) for the TMPRSS2 p.Val160Met polymorphism. Polymorphism was detected using a TaqMan assay. We then analysed the association between the presence of the genetic variant and disease severity and viral load. We did not observe any correlation between the presence of TMPRSS2 genetic variant and the severity of the disease. However, we identified a significant association between the p.Val160Met polymorphism and the SARS-CoV-2 viral load, as estimated by the Ct value of the diagnostic nucleic acid amplification test. Furthermore, we observed a trend of association between the presence of the C allele and the mortality rate in patients with severe COVID-19.

Conclusion: Our data indicate a possible association between TMPRSS2 p.Val160Met polymorphism and SARS-CoV-2 infectivity and the outcome of COVID-19.

Keywords: COVID-19, TMPRSS2, Polymorphism

* Correspondence: delvac.oceandy@manchester.ac.uk
†Laksmi Wulandari, Berliana Hamidah and Cennikon Pakpahan contributed equally to this work.
[17]Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
Full list of author information is available at the end of the article

Background

Coronavirus disease 2019 (COVID-19) is the biggest pandemic in the twenty-first century so far. Since the declaration of the pandemic by the World Health Organization (WHO), more than 110 million cases with more than 2.4 million deaths worldwide have been recorded as per mid-February 2021 [1]. COVID-19 is caused by an infection with the SARS-CoV-2 virus, which typically infects cells in the respiratory tract. The clinical presentations of COVID-19 range widely from asymptomatic infection to lethal pneumonia. It is known that three major factors, i.e. age, gender and the presence of underlying diseases, play a major role in determining COVID-19 severity [2–4]. However, it is not clear whether genetic variability contributes significantly to the clinical outcomes of COVID-19 patients.

One important factor that may play a crucial role in determining COVID-19 severity is the interaction between the virus and the host cells. SARS-CoV-2 infects the host cells by binding with its receptor on the surface of the host cell membrane. The main receptor for the SARS-coronavirus family is the angiotensin-converting enzyme 2 (ACE2) [5]. It is known that the spike (S) protein of SARS-CoV-2 mediates the binding of the virus to the ACE2 protein [6]. Considering the importance of virus receptor binding during the infection, it is logical to hypothesise that genetic variations within the gene encoding ACE2 may be associated with the degree of infection and hence the severity of the disease. Surprisingly, studies have reported no correlation between the genetic variations in the human *ACE2* gene and the severity of COVID-19 [7], as well as the previous severe acute respiratory syndrome (SARS) [8].

In addition to ACE2, several other molecules are also involved in the process of SARS-CoV-2 virus entry. For example, transmembrane protease serine 2 (TMPRSS2) [9] and neuropilin-1 (NRP1) [10] have been identified as co-receptors for SARS-CoV-2 that play a crucial role during virus entry. These molecules are important in mediating virus entry; for example, TMPRSS2 is known to facilitate the cleavage of the S protein, enabling membrane fusion and endocytic entry of the virus particles [11]. This has prompted us to hypothesise that genetic variability within the *TMPRSS2* gene may play a role in determining SARS-CoV-2 infection.

A recent analysis based on computational modelling suggested that out of more than eleven thousand single nucleotide polymorphisms (SNPs) within the human *TMPRSS2* gene (dbSNP, NCBI) only 21 SNPs with minor allele frequency (MAF) between 0.01 and 0.95 were predicted to affect the function of the protein [12]. Of these 21 SNPs, only two SNPs are missense variants (rs12329760 and rs75603675). The rs12329760 polymorphism (also known as p.Val160Met variant) has been shown in several studies to play a role in mediating the risk for prostate cancer, confirming clinical consequences of this genetic variant [13–16]. Therefore, in this study, we focused on studying the association between the p.Val160Met variant of the TMPRSS2 gene and the severity, viral load and clinical outcomes of COVID-19 patients. Although we did not find any correlation between the p.Val160Met polymorphism and disease severity, we observed a possible association between the TMPRSS2 pVal160Met variant and the viral load in COVID-19 patients.

Results

Characteristics of patients

Characteristics of COVID-19 patients included in this study are described in Table 1. Age distributions were significantly different between patients with asymptomatic and mild versus moderate and severe COVID-19. There was a significant difference in the sex distribution with a higher proportion of male patients in the symptomatic groups. Significant differences were observed in the proportions of patients with underlying diseases between the asymptomatic and mild patients versus moderate and severe groups. As expected, the patients in the asymptomatic and mild COVID-19 groups displayed a significantly lower frequency of underlying diseases compared with the moderate and severe groups, including diabetes (P value < 0.001), cardiovascular disease (P value = 0.009) and liver disease (P value = 0.007).

TMPRSS2 p.Val160Met polymorphism and COVID-19 severity

The TMPRSS2 p.Val160Met polymorphism (rs12329760) was successfully detected in all patients. The genotype and allele frequencies of this SNP are shown in Additional file 1. We observed a deviation of the allele frequency from Hardy–Weinberg equilibrium (χ^2 = 6.72, P value = 0.035). However, the frequency of C allele (61.6%) and T allele (38.4%) in this study population seemed to be comparable with the reported frequency in the Asian population (dbSNP, NCBI) (Additional file 1).

The cross-tab analysis for the genotype and severity groups indicated no significant difference in the distribution of TMPRSS2 p.Val160Met polymorphism among the four groups of patients (Table 2). There were higher odds ratios in subjects with CC and CT genotypes to get symptomatic or more severe COVID-19 than those with TT genotype although they did not reach statistical significance (Table 3).

TMPRSS2 p.Val160Met polymorphism and viral load

Next, we analysed the association between polymorphism and the viral load. All of the patients had positive results of the nucleic acid amplification testing (NAAT)

Table 1 Demographic and baseline characteristics

Variables	Asymptomatic (*N*=21)	Mild (*N*=12)	Moderate (*N*=32)	Severe (*N*=30)	All patients (*N*=95)	*P* value chi-square test (unless otherwise stated)
Age (years)	33.9 ± 2.4*	35.6 ± 2.7*	52.3 ± 2.1	48.8 ± 1.5	44.7 ± 1.3	*$P<0.001$ versus moderate and severe groups (ANOVA)
Gender (%)						
Male	8 (38.1%)	10 (83.3%)	19 (59.4%)	23 (76.7%)	60 (63.2%)	0.016
Female	13 (61.9%)	2 (16.7%)	13 (40.6%)	7 (23.3%)	35 (36.8%)	
Underlying diseases (%)						
Diabetes	0	0	9 (28.1%)	12 (40%)	21 (22.1%)	<0.001
CVD	2 (9.5%)	0	13 (40.6%)	10 (33.3%)	25 (26.3%)	0.009
Liver diseases	0	0	4 (12.5%)	9 (30%)	13 (13.7%)	0.007
Kidney diseases	0	0	4 (12.5%)	1 (3.3%)	5 (5.3%)	0.144
Lung diseases	0	0	3 (9.4%)	0	3 (3.2%)	0.107
Others	0	0	3 (9.4%)	2 (6.7%)	5 (5.3%)	0.386

for the SARS-CoV-2 virus. The Ct value was used as the semi-quantitative predictor of the viral load. Since Ct values vary depending on the qPCR system and the methodology of the NAAT, we only focused our analysis on patients with moderate and severe COVID-19. All of the patients in these groups were hospitalised in Dr Soetomo General Academic Hospital; hence, the NAAT was conducted in the same place, i.e. the Clinical Pathology and Microbiology Laboratory, Dr Soetomo General Academic Hospital. We analysed the Ct values of the first NAAT, which were conducted at the time when the patients were admitted to the hospital. A low Ct value is likely associated with a high viral load, whereas a high Ct value is likely to be associated with a low viral load. As illustrated in Fig. 1a, a significant difference was observed in the Ct value between patients with a TT genotype and patients with a CC genotype (P = 0.04), indicating a possible association of this genotype with a higher viral load. The Pearson correlation analysis also indicated a trend of decreasing Ct value with the presence of the C allele (P = 0.08). In contrast, we did not observe any difference and correlation between Ct value and patients' gender (Fig. 1b) as well as between Ct value and age (Fig. 1c). Additionally, there was no difference in Ct value between patients with moderate and severe COVID-19 (Fig. 1d).

TMPRSS2 polymorphism and patients' outcome

During the course of the study, all of the patients with mild COVID-19 recovered, whereas 9.4% of the patients with moderate COVID-19 and 60% of the patients with severe COVID-19 died. When we analysed the association between TMPRSS2 p.Val160Met polymorphism and the patients' outcomes, we did not find any association between the polymorphism and mortality in the moderate COVID-19 group (Table 4). However, we observed a trend of association in the severe group, in which a higher proportion of patients who died of COVID-19 had a CC genotype (P = 0.042 using the linear-by-linear association chi-squared test) (Table 4). We also observed an increasing trend of odds

Table 2 Genotype and allele frequencies of the TMPRSS2 p.Val160Met polymorphism according to COVID-19 severity

	Asymptomatic (*N*=21)		Mild (*N*=12)		Moderate (*N*=32)		Severe (*N*=30)		Chi-square test
	N	%	*N*	%	*N*	%	*N*	%	
Genotype (amino acids)									
CC (Val/Val)	8	38.1	4	33.3	17	53.1	13	43.4	χ^2= 3.11
CT (Val/Met)	7	33.3	5	41.7	11	34.4	10	33.3	*P*=0.79
TT (Met/Met)	6	28.6	3	25	4	12.5	7	23.3	
Allele									
C Allele	23	54.8	13	54.2	45	70.3	36	60	χ^2= 3.51
T Allele	19	45.2	11	45.8	19	29.7	24	40	*P*=0.32

Table 3 Analysis of odds ratio for the risk of symptomatic or more severe COVID-19 in each genotype

	Asymptomatic (*N*=21) vs all symptomatic cases (*N*=74)			Asymptomatic and mild (*N*=33) vs moderate and severe cases (*N*=62)		
Genotype	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
CC	1.821	0.533–6.219	0.335	2.045	0.676–6.185	0.255
CT	1.592	0.447–5.664	0.471	1.432	0.462–4.437	0.573
TT	1	Reference		1	Reference	

ratios of mortality in subjects with CC and CT genotypes (Table 5).

Discussion

This is the first study to demonstrate a possible association between TMPRSS2 p.Val160Met polymorphism and the degree of SARS-CoV-2 viral load as indicated by the Ct value of NAAT in patients with COVID-19. Patients with a CC genotype, which corresponds to the presence of valine amino acid, tend to display a lower Ct value (high viral load). We also found a trend of association between a CC genotype and mortality in a group of patients with severe COVID-19.

It is widely known that the SARS-CoV-2 virus enters the host cells via binding with ACE2, which acts as the main receptor for the viral particles [6, 9, 17]. The spike

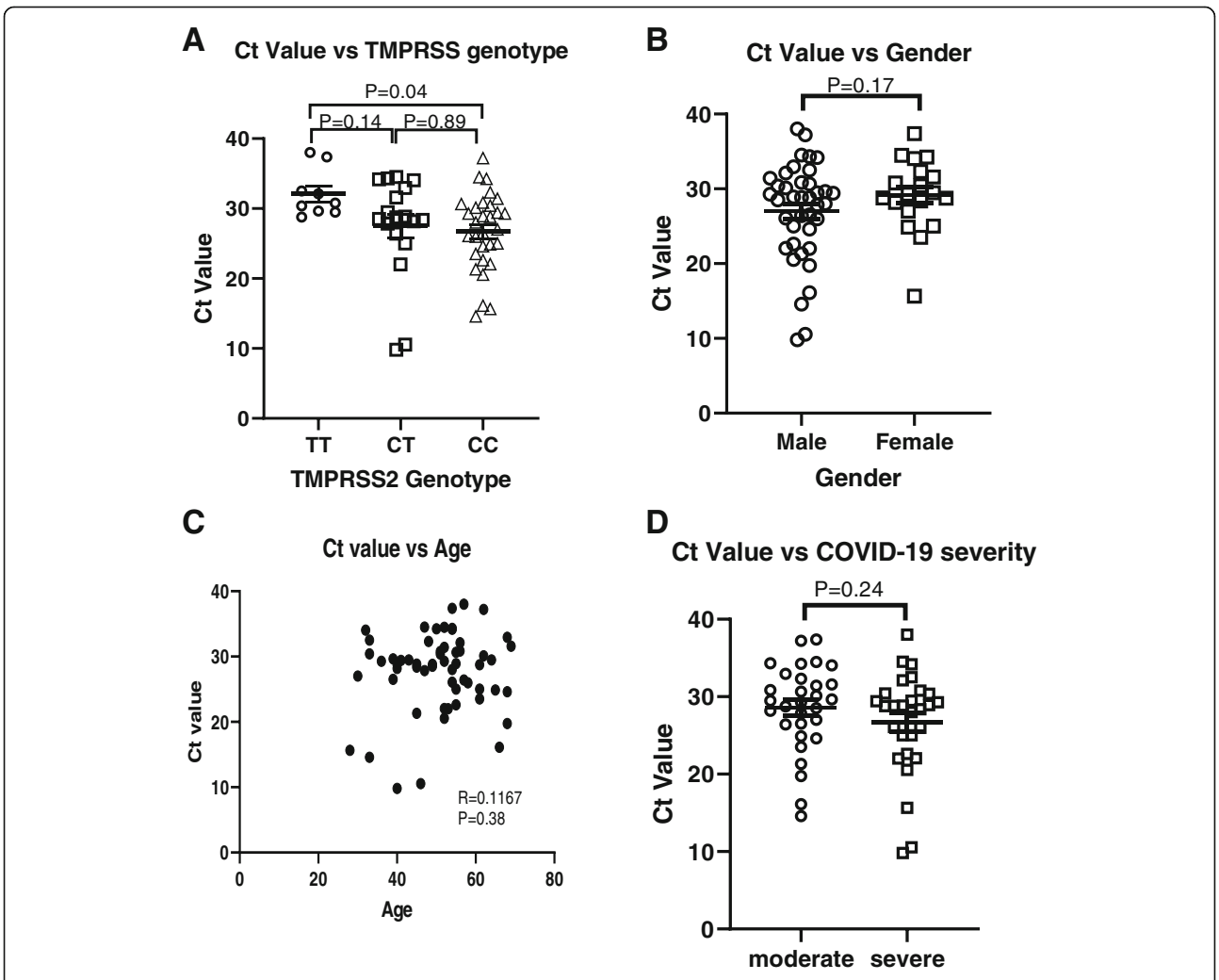

Fig. 1 Analysis of NAAT Ct values of patients with moderate and severe symptoms. **a** Patients with CC genotype displayed significantly lower Ct values of NAAT compared with patients with TT genotype (ANOVA with post hoc multiple comparison test). **b** No difference was observed in Ct values between male and female patients. **c** There was no association between age and Ct value. **d** There was no difference in Ct value between patients with moderate and severe COVID-19

Table 4 Association between TMPRSS2 polymorphism with mortality/survival in patients with moderate-severe COVID-19

	Moderate COVID-19 (*N*=32)		Severe COVID-19 (*N*=30)	
	Recovered (*N*=29, 90.6%)	Died (*N*=3, 9.4%)	Recovered (*N*=12, 30%)	Died (*N*=18, 60%)
Genotype (amino acids)				
CC (Val/Val)	16 (50%)	1 (3.1%)	3 (10 %)	10 (33.3%)
CT (Val/Met)	10 (31.3%)	1 (3.1%)	4 (13.3%)	6 (20 %)
TT (Met/Met)	3 (9.4%)	1 (3.1%)	5 (16.7%)	2 (6.7%)
	Chi-square test *P*=0.498		Chi-square test *P*=0.109	
	Linear-by-linear chi-square association test *P*=0.299		Linear-by-linear chi-square association test *P*=0.042	

(S) protein of the SARS-CoV-2 virus consists of two sub-units: the S1 sub-unit, which is important for virus attachment, and the S2 sub-unit, which is essential for membrane fusion. ACE2 molecule can bind to the S1 protein to promote virus invasion into the host cells [6, 18]. In human, ACE2 is expressed in many organs, such as the upper respiratory tract, alveolar epithelial cells, vascular endothelial cells and macrophages [5].

In addition to ACE2, several other molecules are involved in SARS-CoV-2 virus binding and cell penetration. The S protein needs to be cleaved to activate the endocytic route of virus entry and to enable membrane fusion. It has been reported that several host proteases are involved in the process of S protein breakdown. These include TMPRSS2, cathepsin L, furin [9] and NRP1 [10].

TMPRSS2 is a serine protease that can prime the S protein of SARS-CoV-2 to enable cell penetration [9, 19]. The expression of TMPRSS2 in VeroE6 cells facilitates SARS-CoV-2 virus entry and promotes virus invasion [9]. Notably, treatment with the TMPRSS2 inhibitor (camostat mesylate) significantly reduced SARS-CoV-2 virus infection [9]. Moreover, TMPRSS2 is also involved in SARS-CoV-1 virus infection [20], supporting the idea of the critical role of this molecule in mediating virus entry.

The human *TMPRSS2* gene is located in chromosome 21.q22.3. It encodes protein that contains a transmembrane domain, low-density lipoprotein receptor class A (LDLRA) domain, scavenger receptor cysteine-rich (SRCR) domain and serine protease catalytic domain [21]. At least six nucleotide variants within the human *TMPRSS2* coding region that cause amino acid substitutions have been identified. These include p.Val160Met, p.Gly181Arg, p.Arg240Cys, p.Gly259Ser, p.Pro335Leu and p.Gly432Ala [22]. Of these variants, the p.Val160-Met variant is often associated with diseases, notably prostate cancer. A study conducted on a Japanese population indicated that the TMPRSS2 p.Val160Met variant (also known as Met160Val polymorphism) was associated with the risk of sporadic prostate cancer [16]. Also, a study conducted on 214 patients with prostate cancer demonstrated that the T allele of this variant, which is associated with the presence of Met amino acid, was associated with TMPRSS2-ERG fusion and, thus, might be important in prostate cancer pathogenesis [23].

Our data indicate that in our study population the proportion of the genotypes deviates from the Hardy–Weinberg equilibrium. This deviation could be due to natural selection, non-random mating, genetic drift, or gene flow [24]. In our study population, the deviation was likely due to the higher number of subjects with CC and TT genotypes than the expected values (Additional file 1). However, the frequency of subjects with heterozygous genotype (CT) was lower than the expected value. Therefore, it is unlikely that the deviation was due to natural selection or advantages of a specific allele because the number of subjects with homozygous genotypes of both the T and C alleles was higher than the expected values, implying that there was no specific advantage of either the T or C allele. Thus, it is more likely that the deviation was due to non-random mating or genetic drift, which is more likely to occur in a small study population.

Recent bioinformatic analysis studying the functional effects of nucleotide variants within the human *TMPRSS2* gene revealed that the p.Val160Met variant was the

Table 5 Analysis of odds ratio for the mortality in moderate and severe COVID-19 patients

	Odds ratio of mortality in moderate COVID-19			Odds ratio of mortality in severe COVID-19		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Genotype						
CC	0.188	0.009-3.895	0.241	8.33	1.034-67.14	0.062
CT	0.3	0.014-6.382	0.423	3.75	0.473-29.75	0.335
TT	1	Reference		1	Reference	

most likely variant that might affect TMPRSS2 protein function and stability [12]. Furthermore, a computational analysis to predict the effects of polymorphism on protein structure suggested that the Val160Met substitution might create a pocket protein by influencing several amino acid residues, which might affect TMPRSS2 structure and its role in SARS-CoV-2 cell entry [12]. Possible changes in TMPRSS2 function and/or structure due to the Val160Met substitution might explain our findings on the association of this SNP with the viral load in COVID-19 patients. Alteration of TMPRSS2 function/structure will likely affect the binding of the S protein to ACE2 or the membrane fusion process. Reduction in TMPRSS2 enzymatic activity may decrease the furin cleavage of the S1 protein, which may subsequently decrease S2 fusion to the host's cell membrane. However, further studies at the molecular level are required to prove this hypothesis, for example, by generating recombinant TMPRSS2 proteins bearing the variants and testing them in an in vitro model of SARS-CoV-2 cell infection.

Despite the association between pVal160Met polymorphism and the Ct value, we did not find any correlation between the variant and COVID-19 severity. This might be due to other confounding factors that strongly contribute to the severity of COVID-19. It is believed that factors, such as age [3], gender [25] and pre-existing diseases (hypertension, diabetes, CVD and lung disease) [4], strongly correlate with the risk of severe COVID-19. Further analysis with a larger study population is required to control these confounding variables. Interestingly, in patients with severe COVID-19, we observed a trend of association between this polymorphism and the mortality of COVID-19 patients. However, this requires further confirmation in studies with a larger sample size.

Several studies have found associations between genetic variations in the patient's genome and COVID-19 severity. Many of the reported polymorphisms were related to genes involved in the development of inflammatory response, for example, polymorphisms in genes related to type 1 interferon immunity [26], polymorphisms in X-chromosomal TLR7 [27] and polymorphisms within genes involved in the interleukin 1 signalling pathway [28]. Our finding indicates a correlation between polymorphism in the gene encoding the virus receptor complex, i.e. TMPRSS2, and COVID-19 severity. Our data are consistent with previous reports on TMPRSS2 polymorphisms and COVID-19 severity. Initial whole genome analysis of 322 COVID-19 patients in a Chinese population observed a decreasing allele frequency of the TMPRSS2 rs12329760 variant among patients with severe disease compared with patients with mild COVID-19 [28], indicating the importance of TMPRSS2 in COVID-19. Consistently, studies on Italian COVID-19 patients also demonstrated the role of genetic polymorphisms within the *TMPRSS2* gene in determining COVID-19 severity. An observation on 133 COVID-19 patients found a difference in frequency of this variant in the COVID-19 patient cohort compared with the frequency in the reference databases [29]. In particular, in-depth analysis of available data from the COVID-19 Host Genetic Initiative (HGI) [30] suggested a significant association between TMPRSS2 gene polymorphism rs12329760 with severe/hospitalised COVID-19 [31]. However, further analysis on the available HGI data (https://app.covid19hg.org/) indicated that there was no significant association/difference of polymorphic allele between all SARS-CoV-2-infected subjects and the general population (P=0.569). This data is in line with our finding that the polymorphism may have more significant effects in severe cases of COVID-19.

Together, all of the data indicate a crucial involvement of the *TMPRSS2* genetic variation, the p.Val160Met (rs12329760) in particular, in mediating the severity of COVID-19. This will contribute to the growing body of evidence on the crucial involvement of the host's genetic factor in determining susceptibility to and/or severity of COVID-19.

Conclusions

In summary, this is the first study to demonstrate a possible association between TMPRSS2 p.Val160Met polymorphism and higher viral load in COVID-19 patients. The main limitation of our study is its small sample size. Further large-scale studies are required to validate our findings. Also, by using the Ct value, we can only have an estimate of the viral load. Precise determination of the viral RNA copy number using standard curve qPCR is required to accurately determine the viral load. Mechanistic analysis using a cell culture system is also important to confirm the effects of p.Val160Met on TMPRSS2 protein function. Nevertheless, our finding may provide new insights into the possibility of using this polymorphism as a biomarker or predictor for COVID-19 severity/clinical outcome. Furthermore, our data may also support the idea of targeting TMPRSS2 in COVID-19 therapy, as has been done in some clinical trials [32].

Methods

Study design, patients and data collection

This study was a cross-sectional study conducted from June to August 2020. During this period, a total of 95 patients with COVID-19 were enrolled. Patients with moderate and severe COVID-19 (n = 62, 65.3%) were hospitalised in Dr Soetomo General Academic Hospital, Surabaya, Indonesia, whilst 33 patients (34.7%) with asymptomatic or mild symptoms were treated in Indrapura KOGABWILHAN II Hospital, Surabaya, Indonesia.

The diagnosis was confirmed using the nucleic acid amplification test (NAAT) of the oro-nasopharyngeal swab specimens. For patients with moderate and severe symptoms, the NAAT was performed in the Clinical Pathology and Microbiology Laboratory, Dr Soetomo General Academic Hospital, whereas for asymptomatic patients and patients with mild symptoms, the NAAT was conducted in the Centre for Health Laboratory, Surabaya, as part of the standard procedure for COVID-19 management in East Java Province, Indonesia. This study obtained ethical approval from the Local Ethics Committee of Dr Soetomo General Academic Hospital, Surabaya, Indonesia (0006/LOE/301.4.2/V/2020). All patients have signed the informed consent and agreed to participate in this study.

We clustered patients in three categories of disease severity based on criteria according to the WHO Guideline for COVID-19 Management [33] as follows: (i) mild: characterised by the presence of COVID-19 symptoms that meet the case definition of COVID-19 (fever, persistent cough, fatigue, anorexia, shortness of breath, myalgia, sore throat, nose congestion, headache, diarrhoea, nausea and vomiting, anosmia, ageusia) without evidence of viral pneumonia and hypoxia; (ii) moderate: characterized by the presence of the clinical signs of pneumonia but without any signs of hypoxia ($SpO_2 \geq 93\%$); and (iii) severe: characterized by the presence of the clinical signs of pneumonia and one of the clinical signs of respiratory distress (respiratory rate > 30×/min, severe respiratory distress, or $SpO_2 < 93\%$).

DNA isolation

Heparinized peripheral blood samples were collected and stored in a −80°C freezer before use. DNA extraction was performed using the QIAamp® Blood DNA Midi kit (cat #51185, Qiagen) according to the manufacturer's recommended protocol. DNA concentrations were determined using a microvolume spectrophotometer (NanoDrop Lite, Thermo Fisher Scientific). The procedures were conducted in the Biosafety Level 3 (BSL 3) Laboratory in the Institute of Tropical Disease, Universitas Airlangga, to reduce the risk of COVID-19 transmission.

Polymorphism detection

The TMPRSS2 polymorphism (rs12329760, TMPRSS2 p.Val160Met also known as TMPRSS2 Met160Val polymorphism) was detected using a TaqMan SNP genotyping assay (Cat #4351379, Applied Biosystems, USA) in accordance with the protocol recommended by the manufacturer. Genotyping was performed using real-time polymerase chain reaction (RT-PCR) with VIC and FAM fluorescent reporters to indicate allelic discrimination. The 7500 Fast Real-Time PCR System (Applied Biosystems) was used in conjunction with the 7500 software v2.3 (Life Technologies™, Applied Biosystems) to create the allelic discrimination plot.

Data analysis

Statistical analyses were performed using the IBM SPSS Statistics Software ver. 23 (IBM Corp.) or GraphPad Prism ver. 8 (GraphPad Software, LLC). A chi-squared test was used to examine the Hardy–Weinberg equilibriums and to determine the association between categorical variables in the cross-tabulation data. ANOVA with post hoc multiple comparisons was used to analyse numerical data. A P value less than 0.05 was considered to be statistically significant.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; SARS-CoV-2: SARS coronavirus 2; TMPRSS2: Transmembrane protease serine 2; ACE2: Angiotensin-converting enzyme 2; NRP1: Neuropilin-1; dbSNP: Database of single nucleotide polymorphism; NAAT: Nucleic acid amplification test; SNP: Single nucleotide polymorphism; LDLRA: Lipoprotein receptor class A; SRCR: Scavenger receptor cysteine-rich; CVD: Cardiovascular disease; HGI: Host genetics initiative

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-021-00330-7.

Additional file 1. Genotype and allele frequencies of the TMPRSS2 p.Val160Met polymorphism in all patients.

Acknowledgements

We thank Aldise M. Nastri, Krisnoadi Rahardjo, Rima R. Prasetya, and Jezzy R. Dewantari (Institute of Tropical Disease, Universitas Airlangga) for the support during laboratory work. We thank Astri N. Amalia and Anisa Octaviani for the administration support.

Authors' contributions

L.W, designed the study, managed the funding, supervised the biological sample collection and collected and analysed the clinical data; B.H, performed the DNA extraction and polymorphism detection and wrote the manuscript; C.P: performed the DNA extraction and polymorphism detection and wrote the manuscript; N.S.D, collected blood samples and clinical data; N.D.K, collected blood samples; M.R.W, collected the clinical data; C.O.A, collected blood samples; S, supervised the blood sample collection, D.H, supervised the blood sample collection; DT, designed the study and supervised ethical clearance; CRSP, designed the study and supervised the project; A.E, supervised the project; N.N.T.P, supervised the project; Y.M, supervised the project; M.I.L, supervised the project; K.S, supervised the DNA isolation and polymorphism detection; DO, conceived the original idea, designed the study, performed the data analysis and wrote and edited manuscript. The authors read and approved the final manuscript.

Funding

This work was funded by Mandate Research Grant Special for COVID-19 from Universitas Airlangga (2020).

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

The protocol of the study including biological sample collection and storage of materials and information was approved by the Ethics Committee of Dr Soetomo General Academic Hospital, Surabaya, Indonesia (0006/LOE/301.4.2/V/2020). All patients signed the informed consent form and agreed to participate in this study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga/Dr Soetomo General Academic Hospital, Surabaya, Indonesia. [2]Department of Biomedical Sciences, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [3]Andrology Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [4]Indrapura KOGABWILHAN II Hospital, Surabaya, Indonesia. [5]Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga/Clinical Microbiology Unit, Central Laboratory Installation, Dr Soetomo General Academic Hospital, Surabaya, Indonesia. [6]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [7]Clinical Pathology Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [8]Department of Child Health, Faculty of Medicine, Universitas Airlangga/Dr Soetomo General Academic Hospital, Surabaya, Indonesia. [9]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Airlangga/Dr Soetomo General Academic Hospital, Surabaya, Indonesia. [10]Department of Dermatology Venerology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. [11]Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia. [12]Laboratory of Proteomic, University CoE-Research Center for Bio-Molecule Engineering, Universitas Airlangga, Surabaya, Indonesia. [13]Center for Infectious Diseases, Kobe University Graduate School of Medicine, Kusunoki-cho, Chuo-ku, Kobe, Japan. [14]Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia. [15]Department of Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [16]CRC-ERID, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia. [17]Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK.

Received: 2 March 2021 Accepted: 4 May 2021
Published online: 17 May 2021

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PUBLICATION TYPE

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14739542, 14797364

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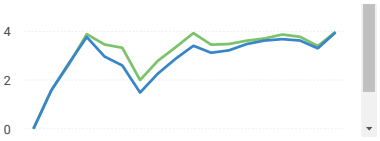

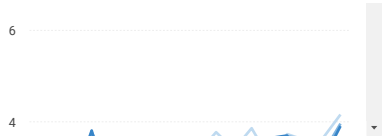

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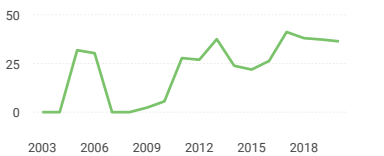

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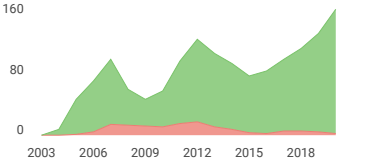

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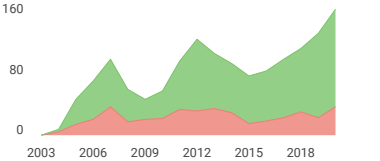

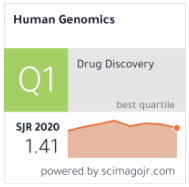

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