biomolecules

an Open Access Journal by MDPI

Indexed in: PubMed | CITESCORE 5.7 | IMPACT FACTOR 6.064

CERTIFICATE OF PUBLICATION

Certificate of publication for the article titled:

Functional and Structural Impact of Deleterious Missense Single Nucleotide Polymorphisms in the NR3C1, CYP3A5, and TNF-α Genes: An In Silico Analysis

Authored by:

Navakanth Raju Ramayanam; Ranjani Manickam; Vijayakumar Thangavel Mahalingam; Khang Wen Goh; Chrismawan Ardianto; Poovi Ganesan; Long Chiau Ming; Rajanandh Muhasaparur Ganesan

Published in:

Biomolecules **2022**, Volume 12, Issue 9, 1307

MDPI Academic Open Access Publishing since 1996

Basel, April 2023

User Menu

Home (/user/myprofile)
Manage Accounts (/user/manage_accounts)
Change Password (/user/chgpwd)
Edit Profile (/user/edit)
Logout (/user/logout)

Submissions Menu

Submit Manuscript (/user/manuscripts/upload)
Display Submitted Manuscripts (/user/manuscripts/status)
Display Co-Authored Manuscripts (/user/manuscripts/co-authored)
English Editing (/user/pre_english_article/status)
Discount Vouchers (/user/discount_voucher)
Invoices (/user/invoices)
LaTex Word Count (/user/get/latex_word_count)

Reviewers Menu

Reviews (/user/reviewer/status)
Volunteer Preferences (/volunteer_reviewer_info/view)

Article Information Overview

Manuscript ID	**biomolecules-1827755**
Status	Website online
DOI	10.3390/biom12091307
Publication Certificate	A4
Banner	Download Banner (PDF) (/publication/articler/banner/917053)
Website Links	Abstract (https://www.mdpi.com/2218-273X/12/9/1307) HTML version (https://www.mdpi.com/2218-273X/12/9/1307/htm) PDF version (https://www.mdpi.com/2218-273X/12/9/1307/pdf) Manuscript (https://www.mdpi.com/2218-273X/12/9/1307/manuscript)
Article type	Article
Title	Functional and Structural Impact of Deleterious Missense Single Nucleotide Polymorphisms in the NR3C1, CYP3A5, and TNF-α Genes: An In Silico Analysis
Journal	*Biomolecules* (https://www.mdpi.com/journal/biomolecules)
Volume	12
Issue	9
Section	Biomacromolecules: Proteins (https://www.mdpi.com/journal/biomolecules/sections/Biomacromolecules_Proteins)
Special Issue	Rare Diseases Associated with SNPs and Protein Structure Modifications (https://www.mdpi.com/journal/biomolecules/special_issues/Rare_SNP_Prot_Str_Mod)
Abstract	Human diseases are generally influenced by SNPs (single nucleotide polymorphisms). The mutations in amino acid residues generated by deleterious SNPs contribute to the structural and functional diversity of the encoded protein. Tumor necrosis factor-α (TNF-α), Glucocorticoid receptor gene (NR3C1), and Cytochrome P450 3A5 (CYP3A5) play a key role in glucocorticoid resistance susceptibility in humans. Possible causative mutations could be used as therapeutic targets and diagnostic markers for glucocorticoid resistance. This study evaluated the missense SNPs of TNF-α, NR3C1, and CYP3A5 to predict their impact on amino acid changes, protein interaction, and functional stability. The protein sequence of dbSNP was obtained and used online in silico method to screen deleterious mutants for the in silico analysis. In the coding regions of TNF-α, NR3C1, and CYP3A5, 14 deleterious mutations were discovered. The protein functional and stability changes in the amino acid between native and mutant energy were identified by analyzing the changes in the hydrogen bonding of these mutants from native, which were all measured using Swiss PDB and PyMOL. F446S and R439K had the highest root-mean-square deviation (RMSD) values among the 14 deleterious mutants. Additionally, the conserved region of amino acid protein interaction was analyzed. This study could aid in the discovery of new detrimental mutations in TNF-α, NR3C1, and CYP3A5, as well as the development of long-term therapy for corticosteroid resistance in several inflammatory diseases. However, more research into the deleterious mutations of the *TNF-α*, *NR3C1*, and *CYP3A5* genes is needed to determine their role in corticosteroid resistance.
Keywords	glucocorticoid resistance; computational study; pharmacogenomic; precision medicine; missense mutation; SNP

Author Information

Submitting Author	Chiau Ming Long

Corresponding Authors	Vijayakumar Thangavel Mahalingam, Khang Wen Goh, Chrismawan Ardianto, Rajanandh Muhasaparur Ganesan
Author #1	Navakanth Raju Ramayanam
Affiliation	1. Department of Pharmacy Practice, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur 603203, India
E-Mail	drnavakanthraju@gmail.com **(co-author email has not been published)**)
Author #2	Ranjani Manickam
Affiliation	2. SRM-DBT Platform for Advanced Life Science Technologies, SRM Institute of Science and Technology, Kattankulathur 603203, India
E-Mail	ranjanim2@srmist.edu.in **(co-author email has not been published)**)
Author #3	Vijayakumar Thangavel Mahalingam
Affiliation	1. Department of Pharmacy Practice, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur 603203, India
E-Mail	vijaypractice@yahoo.com **(corresponding author email)**
Author #4	Khang Wen Goh (https://orcid.org/0000-0001-6686-7019)
Affiliation	3. Faculty of Data Science and Information Technology, INTI International University, Nilai 71800, Malaysia
E-Mail	khangwen.goh@newinti.edu.my **(co-author email has not been published)**)
Author #5	Chrismawan Ardianto (https://orcid.org/0000-0003-3713-7900)
Affiliation	4. Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
E-Mail	chrismawan-a@ff.unair.ac.id **(corresponding author email)**
Author #6	Poovi Ganesan
Affiliation	5. Department of Pharmaceutics, College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences Gorimedu, Puducherry 605006, India
E-Mail	poovinano@gmail.com **(co-author email has not been published)**)
Author #7	Long Chiau Ming
Affiliation	6. PAP Rashidah Sa'adatul Bolkiah Institute of Health Sciences, Universiti Brunei Darussalam, Gadong BE1410, Brunei
E-Mail	chiauming.long@qiu.edu.my **(co-author email has not been published)**)
Author #8	Rajanandh Muhasaparur Ganesan
Affiliation	7. Department of Pharmacy Practice, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai 600116, India
E-Mail	rajanandh.mg@sriramachandra.edu.in **(corresponding author email)**

Manuscript Information

Received Date	6 July 2022
Revised Date	24 August 2022
Accepted Date	31 August 2022
Published Date	16 September 2022
Submission to First Decision (Days)	56
Submission to Publication (Days)	71
Round of Revision	1
Size of PDF	9214 KiB
Word Count	4239
Page Count	18
Figure Count	12
Table Count	7
Reference Count	42
Citations	1

Editor Decision

Decision	Accept in current form
Decision Date	31 August 2022

Review Report

Reviewer 1	Review Report (Round 1) (/user/manuscripts/review/28753299?report=21186056)
Reviewer 2	Review Report (Round 1) (/user/manuscripts/review/28820370?report=21241623)
Reviewer 3	Review Report (Round 1) (/user/manuscripts/review/29383620?report=21695420) Review Report (Round 2) (/user/manuscripts/review/29383620?report=22080792)

APC information

Journal APC:	2,100.00 CHF
Discount Voucher:	97c1fd1c57d9b45e (100.00%) (chiauming.long@qiu.edu.my)
Total Payment Amount:	0.00 CHF

Previously Published Papers

Khotib, J.; Gani, M.A.; Budiatin, A.S.; Lestari, M.L.A.D.; Rahadiansyah, E.; Ardianto, C. Signaling Pathway and Transcriptional Regulation in Osteoblasts during Bone Healing: Direct Involvement of Hydroxyapatite as a Biomaterial. *Pharmaceuticals* **2021**, *14*, 615. doi: 10.3390/ph14070615 (https://doi.org/10.3390/ph14070615)

Gani, M.A.; Budiatin, A.S.; Lestari, M.L.A.D.; Rantam, F.A.; Ardianto, C.; Khotib, J. Fabrication and Characterization of Submicron-Scale Bovine Hydroxyapatite: A Top-Down Approach for a Natural Biomaterial. *Materials* **2022**, *15*, 2324. doi: 10.3390/ma15062324 (https://doi.org/10.3390/ma15062324)

Ayoub, R.; Jilani, J.; Jarrar, Q.; Alani, R.; Ardianto, C.; Goh, K.W.; Ali, D.; Moshawih, S. Synthesis and In-Vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs for Clinical Use. *Molecules* **2022**, *27*, 3023. doi: 10.3390/molecules27093023 (https://doi.org/10.3390/molecules27093023)

Khirfan, F.; Jarrar, Y.; Al-Qirim, T.; Goh, K.W.; Jarrar, Q.; Ardianto, C.; Awad, M.; Al-Ameer, H.J.; Al-Awaida, W.; Moshawih, S.; Ming, L.C. Analgesics Induce Alterations in the Expression of SARS-CoV-2 Entry and Arachidonic-Acid-Metabolizing Genes in the Mouse Lungs. *Pharmaceuticals* **2022**, *15*, 696. doi: 10.3390/ph15060696 (https://doi.org/10.3390/ph15060696)

Moshawih, S.; Lim, A.F.; Ardianto, C.; Goh, K.W.; Kifli, N.; Goh, H.P.; Jarrar, Q.; Ming, L.C. Target-Based Small Molecule Drug Discovery for Colorectal Cancer: A Review of Molecular Pathways and In Silico Studies. *Biomolecules* **2022**, *12*, 878. doi: 10.3390/biom12070878 (https://doi.org/10.3390/biom12070878)

Lai, N.J.-Y.; Ngu, E.-L.; Pang, J.-R.; Wong, K.-H.; Ardianto, C.; Ming, L.C.; Lim, S.-H.; Walvekar, S.G.; Anwar, A.; Yow, Y.-Y. Carrageenophyte *Kappaphycus malesianus* Inhibits Microglia-Mediated Neuroinflammation via Suppression of AKT/NF-*κ*B and ERK Signaling Pathways. *Mar. Drugs* **2022**, *20*, 534. doi: 10.3390/md20080534 (https://doi.org/10.3390/md20080534)

Ling, S.P.; Ming, L.C.; Dhaliwal, J.S.; Gupta, M.; Ardianto, C.; Goh, K.W.; Hussain, Z.; Shafqat, N. Role of Immunotherapy in the Treatment of Cancer: A Systematic Review. *Cancers* **2022**, *14*, 5205. doi: 10.3390/cancers14215205 (https://doi.org/10.3390/cancers14215205)

Budiatin, A.S.; Khotib, J.; Samirah, S.; Ardianto, C.; Gani, M.A.; Putri, B.R.K.H.; Arofik, H.; Sadiwa, R.N.; Lestari, I.; Pratama, Y.A.; Rahadiansyah, E.; Susilo, I. Acceleration of Bone Fracture Healing through the Use of Bovine Hydroxyapatite or Calcium Lactate Oral and Implant Bovine Hydroxyapatite–Gelatin on Bone Defect Animal Model. *Polymers* **2022**, *14*, 4812. doi: 10.3390/polym14224812 (https://doi.org/10.3390/polym14224812)

Jarrar, Q.; Ayoub, R.; Alhussine, K.; Goh, K.W.; Moshawih, S.; Ardianto, C.; Goh, B.H.; Ming, L.C. Prolonged Maternal Separation Reduces Anxiety State and Increases Compulsive Burying Activity in the Offspring of BALB/c Mice. *J. Pers. Med.* **2022**, *12*, 1921. doi: 10.3390/jpm12111921 (https://doi.org/10.3390/jpm12111921)

Khan, F.B.; Uddin, S.; Elderdery, A.Y.; Goh, K.W.; Ming, L.C.; Ardianto, C.; Palakot, A.R.; Anwar, I.; Khan, M.; Owais, M.; Huang, C.-Y.; Daddam, J.R.; Khan, M.A.; Shoaib, S.; Khursheed, M.; Reshadat, S.; Khayat Kashani, H.R.; Mirza, S.; Khaleel, A.A.; Ayoub, M.A. Illuminating the Molecular Intricacies of Exosomes and ncRNAs in Cardiovascular Diseases: Prospective Therapeutic and Biomarker Potential. *Cells* **2022**, *11*, 3664. doi: 10.3390/cells11223664 (https://doi.org/10.3390/cells11223664)

Khan, F.B.; Singh, P.; Jamous, Y.F.; Ali, S.A.; Abdullah; Uddin, S.; Zia, Q.; Jena, M.K.; Khan, M.; Owais, M.; Huang, C.Y.; Chanukuppa, V.; Ardianto, C.; Ming, L.C.; Alam, W.; Khan, H.; Ayoub, M.A. Multifaceted Pharmacological Potentials of Curcumin, Genistein, and Tanshinone IIA through Proteomic Approaches: An In-Depth Review. *Cancers* **2023**, *15*, 249. doi: 10.3390/cancers15010249 (https://doi.org/10.3390/cancers15010249)

Related Papers Published in MDPI Journals

Zahra, A.; Hall, M.; Chatterjee, J.; Sisu, C.; Karteris, E. In Silico Study to Predict the Structural and Functional Consequences of SNPs on Biomarkers of Ovarian Cancer (OC) and BPA Exposure-Associated OC. *Int. J. Mol. Sci.* **2022**, *23*, 1725. doi: 10.3390/ijms23031725 (https://doi.org/10.3390/ijms23031725)

If you have any questions or concerns, please do not hesitate to contact biomolecules@mdpi.com (mailto: biomolecules@mdpi.com).

User Menu

Home (/user/myprofile)
Manage Accounts (/user/manage_accounts)
Change Password (/user/chgpwd)
Edit Profile (/user/edit)
Logout (/user/logout)

Submissions Menu

Submit Manuscript (/user/manuscripts/upload)
Display Submitted Manuscripts (/user/manuscripts/status)
Display Co-Authored Manuscripts (/user/manuscripts/co-authored)
English Editing (/user/pre_english_article/status)
Discount Vouchers (/user/discount_voucher)
Invoices (/user/invoices)
LaTex Word Count (/user/get/latex_word_count)

Reviewers Menu

Reviews (/user/reviewer/status)
Volunteer Preferences (/volunteer_reviewer_info/view)

Journal: Biomolecules (https://www.mdpi.com/journal/biomolecules) (ISSN 2218-273X)

Manuscript ID: biomolecules-1827755

Type: Article

Title: Functional and structural impact of deleterious missense single nucleotide polymorphisms in the NR3C1, CYP3A5, and TNF-α genes: an in silico analysis (https://www.mdpi.com/2218-273X/12/9/1307)

Authors: Navakanth Raju Ramayanam , Ranjani M , Vijayakumar Thangavel Mahalingam * , Khang Wen Goh * , Chrismawan Ardianto * , POOVI GANESAN , Chiau Ming Long , Rajanandh Muhasaparur Ganesan *

Section: Biomacromolecules: Proteins (https://www.mdpi.com/journal/biomolecules/sections/Biomacromolecules_Proteins)

Special Issue: Rare Diseases Associated with SNPs and Protein Structure Modifications (https://www.mdpi.com/journal/biomolecules/special_issues/Rare_SNP_Prot_Str_Mod)

Abstract: Human diseases are generally influenced by SNPs (single nucleotide polymorphisms). The mutations in amino acid residues generated by deleterious SNPs contribute to the structural and functional diversity of the encoded protein. Tumor necrosis factor-α (TNF-α), Glucocorticoid receptor gene (NR3C1), and Cytochrome P450 3A5 (CYP3A5) play a key role in glucocorticoid resistance susceptibility in humans. Possible causative mutations could be used as therapeutic targets and diagnostic markers for glucocorticoid resistance. This study evaluated the missense SNPs of TNF-α, NR3C1, and CYP3A5 to predict their impact on amino acid changes, protein interaction, and functional stability. The protein sequence of dbSNP was obtained and used online in silico method to screen deleterious mutants for the in silico analysis. In the coding regions of TNF-α, NR3C1, and CYP3A5, 14 deleterious mutations were discovered. The protein functional and stability changes in the amino acid between native and mutant energy were identified by analyzing the changes in hydrogen bonding of these mutants from native, which were all measured using Swiss PDB and PyMOL. F446S and R439K had the highest root-mean-square deviation (RMSD) values among the 14 deleterious mutants. Additionally, the conserved region of amino acid protein interaction was analyzed. This study could aid in the discovery of new detrimental mutations in TNF-α, NR3C1, and CYP3A5, as well as the development of long-term therapy for corticosteroid resistance in several inflammatory diseases. However, more research into the deleterious mutations of the TNF-α, NR3C1, and CYP3A5 genes is needed to determine their role in corticosteroid resistance.

The coverletter for this review report has been saved in the database. You can safely close this window.

Authors' Responses to Reviewer's Comments (Reviewer 1)

Author's Notes

Dear reviewer,

We would like to thank you for your careful and thorough reading of this manuscript as well as for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have carefully edited the manuscript according to your inputs. We truly hope that the revised manuscript is clear to follow. The response and amendment for each comment are as below.

REVIEWER 1

The role of missense SNPs of TNF-α, NR3C1, and CYP3A5 generated for the treatment and diagnosis of the most significant corticosteroid resistance in several inflammatory diseases is discussed in the manuscript by Ramayanam et al., along with an explanation of its therapeutic importance. The manuscript is effectively written. The following minor correction must be made to the manuscript before it can be accepted:

- Results and Discussion part, line 8- nSNPs misused

Reply: Thank you so much for pointing it out. As suggested by the reviewer, the correction has been made

- Results and Discussion part, line 34- nsSNPS misused

Reply: Thank you so much for your comment. As suggested by the reviewer, the correction has been made

- Correct Reference 10.

Reply: Thank you so much for pointing it out. As suggested by the reviewer, the reference has been corrected

Review Report Form

Quality of English Language
( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	( )	(x)	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

The role of missense SNPs of TNF-α, NR3C1, and CYP3A5 generated for the treatment and diagnosis of the most significant corticosteroid resistance in several inflammatory diseases is discussed in the manuscript by Ramayanam et al., along with an explanation of its therapeutic importance. The manuscript is effectively written. The following minor correction must be made to the manuscript before it can be accepted:

1 Results and Discussion part, line 8- nSNPs misused

2 Results and Discussion part, line 34- nsSNPS misused

3 Correct Reference 10.

peer-review-21186056.v1.pdf (/user/review/displayFile/28753299/XwmGF4TA?file=review&report=21186056)

Submission Date 06 July 2022

Date of this review 01 Aug 2022 07:58:38

User Menu

Home (/user/myprofile)
Manage Accounts (/user/manage_accounts)
Change Password (/user/chgpwd)
Edit Profile (/user/edit)
Logout (/user/logout)

Submissions Menu

Submit Manuscript (/user/manuscripts/upload)
Display Submitted Manuscripts (/user/manuscripts/status)
Display Co-Authored Manuscripts (/user/manuscripts/co-authored)
English Editing (/user/pre_english_article/status)
Discount Vouchers (/user/discount_voucher)
Invoices (/user/invoices)
LaTex Word Count (/user/get/latex_word_count)

Reviewers Menu

Reviews (/user/reviewer/status)
Volunteer Preferences (/volunteer_reviewer_info/view)

Journal: Biomolecules (https://www.mdpi.com/journal/biomolecules) (ISSN 2218-273X)
Manuscript ID: biomolecules-1827755
Type: Article

Title: Functional and structural impact of deleterious missense single nucleotide polymorphisms in the NR3C1, CYP3A5, and TNF-α genes: an in silico analysis (https://www.mdpi.com/2218-273X/12/9/1307)

Authors: Navakanth Raju Ramayanam , Ranjani M , Vijayakumar Thangavel Mahalingam * , Khang Wen Goh * , Chrismawan Ardianto * , POOVI GANESAN , Chiau Ming Long , Rajanandh Muhasaparur Ganesan *

Section: Biomacromolecules: Proteins (https://www.mdpi.com/journal/biomolecules/sections/Biomacromolecules_Proteins)
Special Issue: Rare Diseases Associated with SNPs and Protein Structure Modifications (https://www.mdpi.com/journal/biomolecules/special_issues/Rare_SNP_Prot_Str_Mod)

Abstract: Human diseases are generally influenced by SNPs (single nucleotide polymorphisms). The mutations in amino acid residues generated by deleterious SNPs contribute to the structural and functional diversity of the encoded protein. Tumor necrosis factor-α (TNF-α), Glucocorticoid receptor gene (NR3C1), and Cytochrome P450 3A5 (CYP3A5) play a key role in glucocorticoid resistance susceptibility in humans. Possible causative mutations could be used as therapeutic targets and diagnostic markers for glucocorticoid resistance. This study evaluated the missense SNPs of TNF-α, NR3C1, and CYP3A5 to predict their impact on amino acid changes, protein interaction, and functional stability. The protein sequence of dbSNP was obtained and used online in silico method to screen deleterious mutants for the in silico analysis. In the coding regions of TNF-α, NR3C1, and CYP3A5, 14 deleterious mutations were discovered. The protein functional and stability changes in the amino acid between native and mutant energy were identified by analyzing the changes in hydrogen bonding of these mutants from native, which were all measured using Swiss PDB and PyMOL. F446S and R439K had the highest root-mean-square deviation (RMSD) values among the 14 deleterious mutants. Additionally, the conserved region of amino acid protein interaction was analyzed. This study could aid in the discovery of new detrimental mutations in TNF-α, NR3C1, and CYP3A5, as well as the development of long-term therapy for corticosteroid resistance in several inflammatory diseases. However, more research into the deleterious mutations of the TNF-α, NR3C1, and CYP3A5 genes is needed to determine their role in corticosteroid resistance.

The coverletter for this review report has been saved in the database. You can safely close this window.

Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes

Dear reviewer,

We would like to thank you for your careful and thorough reading of this manuscript as well as for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have carefully edited the manuscript according to your inputs. We truly hope that the revised manuscript is clear to follow. The response and amendment for each comment are as below.

REVIEWER 2

The subject and aim of this study would be of interest for readers of Biomacromolecules, however, the current form should be revised in some points.

Please disscsuss , if selected SNPs by in silico analysis were tested in previous case-control studies?

Reply: Thank you so much for pointing it out. These SNPs are not tested in the previous case control studies. This has been included in the revised manuscript.

Review Report Form

Quality of English Language

( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
( ) English language and style are fine/minor spell check required
(x) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable

Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

The subject and aim of this study would be of interest for readers of Biomacromolecules, however, the current form should be revised in some points.

Please disscsuss , if selected SNPs by in silico analysis were tested in previous case-control studies?

Submission Date 06 July 2022

Date of this review 06 Aug 2022 23:11:33

User Menu

Home (/user/myprofile)
Manage Accounts (/user/manage_accounts)
Change Password (/user/chgpwd)
Edit Profile (/user/edit)
Logout (/user/logout)

Submissions Menu

Submit Manuscript (/user/manuscripts/upload)
Display Submitted Manuscripts (/user/manuscripts/status)
Display Co-Authored Manuscripts (/user/manuscripts/co-authored)
English Editing (/user/pre_english_article/status)
Discount Vouchers (/user/discount_voucher)
Invoices (/user/invoices)
LaTex Word Count (/user/get/latex_word_count)

Reviewers Menu

Reviews (/user/reviewer/status)
Volunteer Preferences (/volunteer_reviewer_info/view)

Journal: Biomolecules (https://www.mdpi.com/journal/biomolecules) (ISSN 2218-273X)
Manuscript ID: biomolecules-1827755
Type: Article

Title: Functional and structural impact of deleterious missense single nucleotide polymorphisms in the NR3C1, CYP3A5, and TNF-α genes: an in silico analysis (https://www.mdpi.com/2218-273X/12/9/1307)

Authors: Navakanth Raju Ramayanam , Ranjani M , Vijayakumar Thangavel Mahalingam * , Khang Wen Goh * , Chrismawan Ardianto * , POOVI GANESAN , Chiau Ming Long , Rajanandh Muhasaparur Ganesan *

Section: Biomacromolecules: Proteins (https://www.mdpi.com/journal/biomolecules/sections/Biomacromolecules_Proteins)
Special Issue: Rare Diseases Associated with SNPs and Protein Structure Modifications (https://www.mdpi.com/journal/biomolecules/special_issues/Rare_SNP_Prot_Str_Mod)

Abstract: Human diseases are generally influenced by SNPs (single nucleotide polymorphisms). The mutations in amino acid residues generated by deleterious SNPs contribute to the structural and functional diversity of the encoded protein. Tumor necrosis factor-α (TNF-α), Glucocorticoid receptor gene (NR3C1), and Cytochrome P450 3A5 (CYP3A5) play a key role in glucocorticoid resistance susceptibility in humans. Possible causative mutations could be used as therapeutic targets and diagnostic markers for glucocorticoid resistance. This study evaluated the missense SNPs of TNF-α, NR3C1, and CYP3A5 to predict their impact on amino acid changes, protein interaction, and functional stability. The protein sequence of dbSNP was obtained and used online in silico method to screen deleterious mutants for the in silico analysis. In the coding regions of TNF-α, NR3C1, and CYP3A5, 14 deleterious mutations were discovered. The protein functional and stability changes in the amino acid between native and mutant energy were identified by analyzing the changes in hydrogen bonding of these mutants from native, which were all measured using Swiss PDB and PyMOL. F446S and R439K had the highest root-mean-square deviation (RMSD) values among the 14 deleterious mutants. Additionally, the conserved region of amino acid protein interaction was analyzed. This study could aid in the discovery of new detrimental mutations in TNF-α, NR3C1, and CYP3A5, as well as the development of long-term therapy for corticosteroid resistance in several inflammatory diseases. However, more research into the deleterious mutations of the TNF-α, NR3C1, and CYP3A5 genes is needed to determine their role in corticosteroid resistance.

The coverletter for this review report has been saved in the database. You can safely close this window.

Authors' Responses to Reviewer's Comments (Reviewer 3)

Author's Notes

Dear reviewer,

We would like to thank you for your careful and thorough reading of this manuscript as well as for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have carefully edited the manuscript according to your inputs. We truly hope that the revised manuscript is clear to follow. The response and amendment for each comment are as below.

REVIEWER 3

The prediction of mutagenesis was conducted with homology modeling software and as I can see, the authors have conducted the analysis of the surface accessibility, and amino acid residues with standard sequence analysis software.

However, those analysis did not guarantee the mutated protein stability. The significance of the SNP could only be guaranteed of the mutated protein has elicited acceptable and significant stability. This, for example, happens in sickle cell anemia, when the mutated protein exist in the blood.

You can only examine this condition with molecular dynamics methods, especially liaising with the RMSF or protein flexibility parameter. If you want to do it fast and with low computational power, please kindly use online software such as this one:

http://biocomp.chem.uw.edu.pl/CABSflex2

Reply: Thanks for the valuable suggestion, in this study we focused on the deleterious mutations of the TNF-α, NR3C1, and CYP3A5 genes is needed to determine their role in corticosteroid resistance. However we will consider this valuable suggestion for our future work.

Review Report Form

Quality of English Language
( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	( )	(x)	( )	( )
Are the methods adequately described?	( )	(x)	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

The prediction of mutagenesis was conducted with homology modeling software and as I can see, the authors have conducted the analysis of the surface accessibility, and amino acid residues with standard sequence analysis software.

However, those analysis did not guarantee the mutated protein stability. The significance of the SNP could only be guaranteed of the mutated protein has elicited acceptable and significant stability. This, for example, happens in sickle cell anemia, when the mutated protein exist in the blood.

You can only examine this condition with molecular dynamics methods, especially liaising with the RMSF or protein flexibility parameter. If you want to do it fast and with low computational power, please kindly use online software such as this one:

http://biocomp.chem.uw.edu.pl/CABSflex2

Submission Date 06 July 2022

Date of this review 16 Aug 2022 10:38:45

User Menu

Home (/user/myprofile)
Manage Accounts (/user/manage_accounts)
Change Password (/user/chgpwd)
Edit Profile (/user/edit)
Logout (/user/logout)

Submissions Menu

Submit Manuscript (/user/manuscripts/upload)
Display Submitted Manuscripts (/user/manuscripts/status)
Display Co-Authored Manuscripts (/user/manuscripts/co-authored)
English Editing (/user/pre_english_article/status)
Discount Vouchers (/user/discount_voucher)
Invoices (/user/invoices)
LaTex Word Count (/user/get/latex_word_count)

Reviewers Menu

Reviews (/user/reviewer/status)
Volunteer Preferences (/volunteer_reviewer_info/view)

Journal	Biomolecules (https://www.mdpi.com/journal/biomolecules) (ISSN 2218-273X)
Manuscript ID	biomolecules-1827755
Type	Article
Title	Functional and structural impact of deleterious missense single nucleotide polymorphisms in the NR3C1, CYP3A5, and TNF-α genes: an in silico analysis (https://www.mdpi.com/2218-273X/12/9/1307)
Authors	Navakanth Raju Ramayanam , Ranjani M , Vijayakumar Thangavel Mahalingam * , Khang Wen Goh * , Chrismawan Ardianto * , POOVI GANESAN , Chiau Ming Long , Rajanandh Muhasaparur Ganesan *
Section	Biomacromolecules: Proteins (https://www.mdpi.com/journal/biomolecules/sections/Biomacromolecules_Proteins)
Special Issue	Rare Diseases Associated with SNPs and Protein Structure Modifications (https://www.mdpi.com/journal/biomolecules/special_issues/Rare_SNP_Prot_Str_Mod)
Abstract	Human diseases are generally influenced by SNPs (single nucleotide polymorphisms). The mutations in amino acid residues generated by deleterious SNPs contribute to the structural and functional diversity of the encoded protein. Tumor necrosis factor-α (TNF-α), Glucocorticoid receptor gene (NR3C1), and Cytochrome P450 3A5 (CYP3A5) play a key role in glucocorticoid resistance susceptibility in humans. Possible causative mutations could be used as therapeutic targets and diagnostic markers for glucocorticoid resistance. This study evaluated the missense SNPs of TNF-α, NR3C1, and CYP3A5 to predict their impact on amino acid changes, protein interaction, and functional stability. The protein sequence of dbSNP was obtained and used online in silico method to screen deleterious mutants for the in silico analysis. In the coding regions of TNF-α, NR3C1, and CYP3A5, 14 deleterious mutations were discovered. The protein functional and stability changes in the amino acid between native and mutant energy were identified by analyzing the changes in hydrogen bonding of these mutants from native, which were all measured using Swiss PDB and PyMOL. F446S and R439K had the highest root-mean-square deviation (RMSD) values among the 14 deleterious mutants. Additionally, the conserved region of amino acid protein interaction was analyzed. This study could aid in the discovery of new detrimental mutations in TNF-α, NR3C1, and CYP3A5, as well as the development of long-term therapy for corticosteroid resistance in several inflammatory diseases. However, more research into the deleterious mutations of the TNF-α, NR3C1, and CYP3A5 genes is needed to determine their role in corticosteroid resistance.

Review Report Form

Quality of English Language

( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	(x)	( )	( )	( )
Are the conclusions supported by the results?	(x)	( )	( )	( )

Comments and Suggestions for Authors	The revisions are okay
Submission Date	06 July 2022
Date of this review	30 Aug 2022 05:15:45