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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



Basel, April 2023



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		genes is needed to determine their role in corticosteroid resistance.		
	Keywords	glucocorticoid resistance; computational study; pharmacogenomic; precision medicine; missense mutation; SNP		
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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 ^

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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)

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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)

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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)

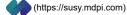
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Author's Notes Dear reviewer,

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

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Comments and The role of missense SNPs of TNF- α , NR3C1, and CYP3A5 generated for the treatment and Suggestions for diagnosis of the most significant corticosteroid resistance in several inflammatory diseases is Authors 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:

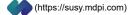
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		We would like to thank you for your careful and thorough reading of this manuscript as well as for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have carefully edited the manuscript 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,

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.

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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.

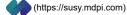
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Manage Accounts	Manuscript ID	biomolecules-1827755				
(/user/manage_accounts)	Туре	Article				
Change Password (/user/chgpwd)	Title	Functional and structural impact of deleterious missense single nucleotide polymorphisms in the NR3C1, CYP3A5, and TNF- α genes: an in silico analysis (https://www.mdpi.com/2218-				
Edit Profile (/user/edit)		273X/12/9/1307)				
Logout (/user/logout)	Authors	Navakanth Raju Ramayanam , Ranjani M , Vijayakumar Thangavel Mahalingam * , Khang Wen Goh * , Chrismawan Ardianto * , POOVI GANESAN , Chiau Ming Long , Rajanandh Muhasaparur Ganesan *				
✓Submissions Menu	Section	Biomacromolecules: Proteins (https://www.mdpi.com/journal/biomolecules/sections/Biomacromolecules_Proteins)				
Submit Manuscript (/user/manuscripts/upload)	Special Issue	Rare Diseases Associated with SNPs and Protein Structure Modifications (https://www.mdpi.com/journal/biomolecules/special issues/Rare SNP Prot Str Mod)				
Display Submitted Manuscripts (/user/manuscripts/status)	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				
Display Co-Authored Manuscripts (/user/manuscripts/co- authored)		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				
English Editing (/user/pre_english_article/status)		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				
Discount Vouchers (/user/discount_voucher)		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				
Invoices (/user/invoices)		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				
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∼Reviewers Menu		their role in corticosteroid resistance.				
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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)	()	()

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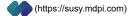
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Submission Date 06 July 2022 16 Aug 2022 10:38:45 Date of this review

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	(/volunteer_reviewer_info/view)	Quality of English	()	English very difficult to understand/incomprehensible
		Language	()	Extensive editing of English language and style required
			()	Moderate English changes required

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Are the methods adequately described?			()	()	()
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				