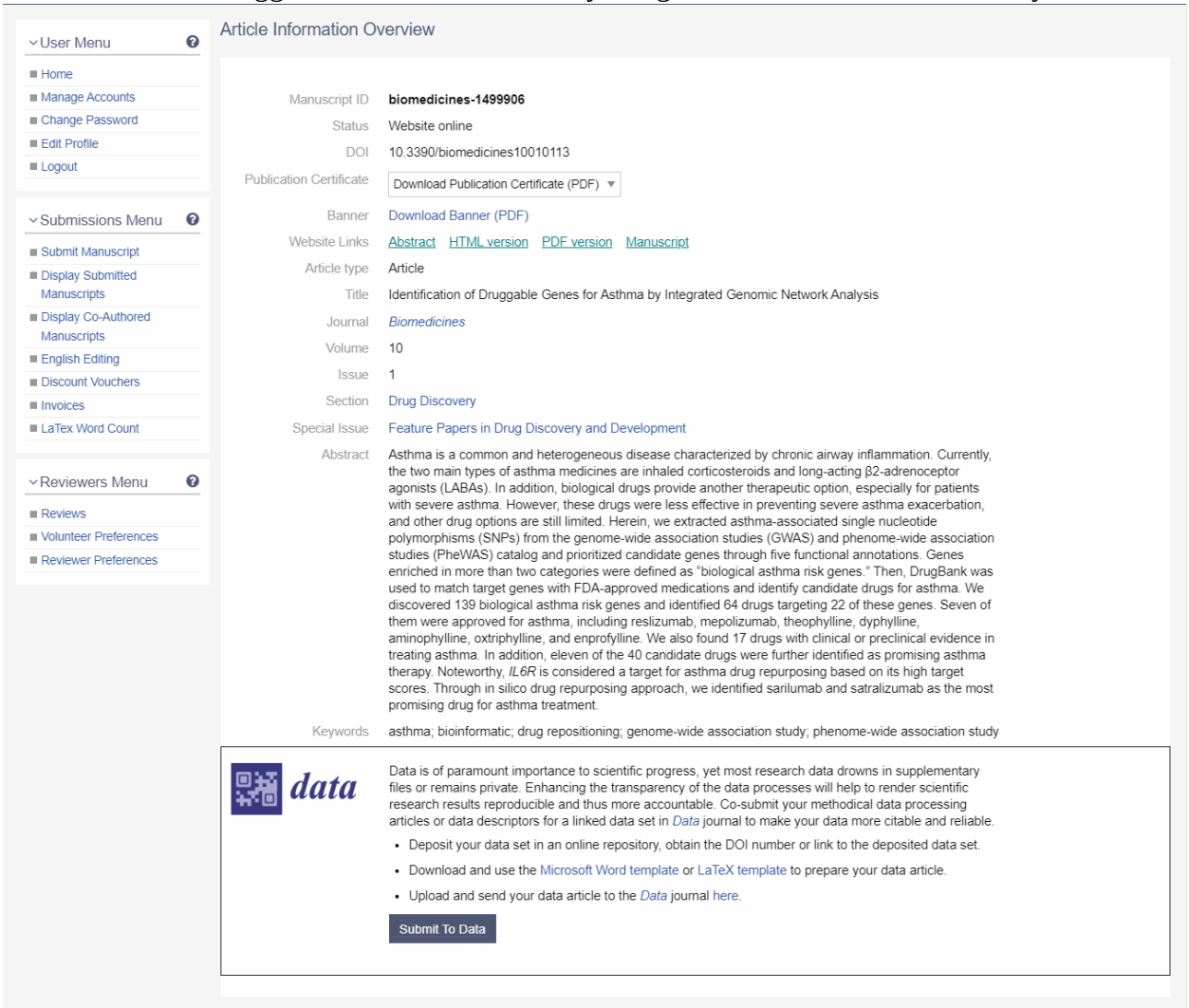
History Artikel

Identification of Druggable Genes for Asthma by Integrated Genomic Network Analysis



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Article Information Overview

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Title	Identification of Druggable Genes for Asthma by Integrated Genomic Network Analysis
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Abstract	Asthma is a common and heterogeneous disease characterized by chronic airway inflammation. Currently, the two main types of asthma medicines are inhaled corticosteroids and long-acting β2-adrenoceptor agonists (LABAs). In addition, biological drugs provide another therapeutic option, especially for patients with severe asthma. However, these drugs were less effective in preventing severe asthma exacerbation, and other drug options are still limited. Herein, we extracted asthma-associated single nucleotide polymorphisms (SNPs) from the genome-wide association studies (GWAS) and phenome-wide association studies (PheWAS) catalog and prioritized candidate genes through five functional annotations. Genes enriched in more than two categories were defined as "biological asthma risk genes." Then, DrugBank was used to match target genes with FDA-approved medications and identify candidate drugs for asthma. We discovered 139 biological asthma risk genes and identified 64 drugs targeting 22 of these genes. Seven of them were approved for asthma, including reslizumab, mepolizumab, theophylline, dyphylline, aminophylline, oxtriphylline, and enprofylline. We also found 17 drugs with clinical or preclinical evidence in treating asthma. In addition, eleven of the 40 candidate drugs were further identified as promising asthma therapy. Noteworthy, *IL6R* is considered a target for asthma drug repurposing based on its high target scores. Through in silico drug repurposing approach, we identified sarilumab and satralizumab as the most promising drug for asthma treatment.
Keywords	asthma; bioinformatic; drug repositioning; genome-wide association study; phenome-wide association study

data

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Review Report

Reviewer 1	Review Report (Round 1) Review Report (Round 2)
Reviewer 2	Review Report (Round 1)
Reviewer 3	Review Report (Round 1) Review Report (Round 2)

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Komentar reviewer 1 tahap 1:

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

Author's Notes	Please see the attachment
Author's Notes File	Report Notes

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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

Dear Authors,

I Have read the manuscript and I send you my comments:

1) Introduction: line 60-62: please delete "To date, aspirin has been successfully used as an antiplatelet drug and colorectal cancer therapy by drug repurposing. Aspirin has been used initially as Non-steroidal anti-inflammatory drugs (NSAIDs) in treating various pain and inflammatory disorders [15]. "

2) Methods: please clarfy methods used inn this study

3) Results: please add IL-17

2) Discussion: line 195 please add PMID: 17044077;

line 209 please add PMID: 23510472

Submission Date	01 December 2021
Date of this review	05 Dec 2021 21:35:57

Komentar reviewer 2 tahap 1

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

Author's Notes: Please see the attachment

Author's Notes File: Report Notes

Review Report Form

Quality of English Language
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(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)	( )	( )	( )
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: In the manuscript by Adikusuma et al., the authors investigated the use of GWAS and PheWas databases to identify the asthma risk loci that could guide the drug discovery. This is an interesting study and potentially, this approach could be used for personalized medicine. As the authors mentioned, this study need a further *in-vitro* functional studies to predict clinical application.

Submission Date: 01 December 2021

Date of this review: 12 Dec 2021 12:12:44

Komentar reviewer 3 tahap 1

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

Author's Notes: Please see the attachment

Author's Notes File: Report Notes

Review Report Form

Quality of English Language
( ) English very difficult to understand/incomprehensible
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( ) 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)	( )	( )
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

First of all, congratulations to the authors for their work, which opens up interesting new avenues of treatment in asthmatic disease. However, I would like to point out some improvements that I believe will enhance the focus of the article.

1.- The first sentence of the article, where the authors state that "Asthma is the most severe inflammatory disorder of the lung" is, I think, rather debatable. It should be rewritten in a less pretentious way.

2.- In both the abstract and the introduction, the authors state that "Currently, the two main types of asthma medicines are inhaled corticosteroids and long-acting β2-adrenoceptor agonists (LABAs)", however, the authors do not include the third major group which is constituted by biologic drugs (specifically monoclonal antibodies) against different targets.

3.- At no point in the introduction or the article do the authors cite the GINA (The Global Initiative for Asthma) Guidelines or Reports. Their latest edition of 2021 should be cited and included in the article, mentioning also the different phenotypes within the asthmatic disease.

4.- Section "2.4 Statistical analysis" should be updated. The authors indicate only the programs used, but do not describe the statistical methods used in the work.

5.- Table 1 represents a result of the authors' research and should therefore be included in this section and not in the discussion.

6.- The discussion could be more elaborated, taking into account the different asthma phenotypes. A critical discussion of previous failures should also be included: for example, a critical reference should be made to other drugs that have not been successful in the treatment of asthma after repositioning, as was recently the case with Risankizumab in Severe Asthma: N Engl J Med 2021; 385:1669-1679. DOI: 10.1056/NEJMoa2030880.

7.- In the discussion, the last sentence "In sum, the anti-IL6R (Sarilumab and Satralizumab) therapy could become novel asthma treatment options" should be rewritten. The authors should lower the expectations of their proposal given that neither further in vitro experiments nor experiments in animal models have been carried out.

8.- The bibliography should be updated as there is not a single citation of articles published in 2021, and at least include the two named in this revision.

Submission Date: 01 December 2021

Date of this review: 14 Dec 2021 11:05:53

Merespon terhadap saran dan masukan dari para reviewer:

December 22, 2021

Dear Editors,

We appreciate this opportunity to submit our revised manuscript: "**Identification of druggable genes for asthma by integrated genomic network analysis**" which we are submitting for consideration for publication as Original Research article in "***Biomedicines"*** **(Manuscript ID: biomedicines-1499906)**. We would like to thank the reviewers for the constructive and insightful comments. Here, we are sending our revised manuscript in accordance with the comments given by the reviewers. We have carefully examined the raised questions and have answered or made changes accordingly. The revised parts are highlighted as red color. We believe that the manuscript is greatly improved by the revisions. Thank you very much for your consideration of our work. Hope very much these revisions are adequate. We appreciate your assistance and are looking forward to hearing from you.

Sincerely yours,

Wei-Chiao Chang (D.Phil.; Oxon)
Professor, Department of Clinical Pharmacy,
Taipei Medical University, Taiwan
250 Wu-Hsing Street, Taipei 110, Taiwan

Reviewer 1

1. Introduction: line 60-62: please delete "To date, aspirin has been successfully used as an antiplatelet drug and colorectal cancer therapy by drug repurposing. Aspirin has been used initially as Non-steroidal anti-inflammatory drugs (NSAIDs) in treating various pain and inflammatory disorders [15]. "
   Answer: We thank you for the suggestions. We have deleted the sentence according to the reviewer's suggestions.

2. Methods: please clarify the methods used in this study
   Answer: We sincerely appreciate the reviewer's comments. In the present study, we first acquired a list of asthma-associated SNPs from the GWAS and PheWAS catalog. The SNPs were then extended to asthma risk genes using HaploReg v4.1. The list of genes were prioritized by a scoring system using five functional annotations: (1) Genes containing missense/nonsense variants, which a single base change causes a substitution of a different amino acid in the resulting protein. (2) Genes containing an SNP with cis-eQTL effect. The polymorphism is associated with a change in gene expression in the target tissue, resulting in biological implications. In our analyses, we set the lung as the target tissue. (3) Genes that were significantly enriched in the over-representation analysis of knockout mice. (4) Genes with protein-protein interactions (PPIs) that are involved in the biological protein networks related to asthma pathogenesis. (5) Genes involved in the enriched pathway using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. The cut-off points for statistical significance were mentioned in the method. Each annotation corresponded to one point. Based on the number of fulfilled criteria, an asthma risk gene can obtain a score from 1 to 5. We defined the genes that were annotated to meet more than or equal to two criteria (score ≥ 2) as "biological asthma risk genes". This scoring system has also been utilized by Yukinori Okada et al. to prioritize genes related to Rheumatoid Arthritis disease and find the candidate drugs for repurposing. The biological asthma risk genes were then mapped to DrugBank to find candidate drugs. ClinicalTrial.gov and PubMed literature reviews were done manually to identify the most promising drug for Asthma.

3. Results: please add IL-17
   Answer: According to our study pipeline, a total of seven promising targets were identified, including *HMGCR*, *PIK3CD*, *CD86*, *BCR*, *NOS1*, *IL6R*, and *ADORA1*. Unfortunately, *IL-17* was not identified as a candidate target for Asthma.

4. Discussion: line 195 please add PMID: 17044077; line 209 please add PMID: 23510472
   Answer: Thank you for the suggestions. We have already added the reference as suggested by the reviewer (PMID: 17044077 line 222 and PMID: 23510472 line 242).

References

1. Okada, Y.; Wu, D.; Trynka, G.; Raj, T.; Terao, C.; Ikari, K. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* **2013**, *506*, 376–381, doi:10.1038/nature12873.
2. Pelaia, G.; Gallelli, L.; D'agostino, B.; Vatrella, A.; Cuda, G.; Fratto, D.; Renda, T.; Galderisi, U.; Piegari, E.; Crimi, N.; et al. Effects of TGF-b and Glucocorticoids on Map

Kinase Phosphorylation, IL-6/IL-11 Secretion and Cell Proliferation in Primary Cultures of Human Lung Fibroblasts. *J. Cell. Physiol.* **2006**, *211(3)*, 736–747, doi:10.1002/JCP.

3. Falcone, D.; Gallelli, L.; Virgilio, A. Di; Tucci, L.; Scaramuzzino, M.; Terracciano, R.; Pelaia, G. Effects of simvastatin and rosuvastatin on RAS protein , matrix metalloproteinases and NF- j B in lung cancer and in normal pulmonary tissues. *Cell Prolif.* **2013**, *46*, 172–182, doi:10.1111/cpr.12018.

Reviewer 2

In the manuscript by Adikusuma et al., the authors investigated the use of GWAS and PheWas databases to identify the asthma risk loci that could guide the drug discovery. This is an interesting study and potentially, this approach could be used for personalized medicine. As the authors mentioned, this study needs a further *in-vitro* functional studies to predict clinical application.

Answer: Many thanks for the reviewer comments. This approach can narrow down the candidate drugs before conducting a clinical trial. We believe it can open up new avenues for the drug discovery process and provide potential gene targets and drug candidates for the drug repurposing and treatment of Asthma.

Reviewer 3

First of all, congratulations to the authors for their work, which opens up interesting new avenues of treatment in asthmatic disease. However, I would like to point out some improvements that I believe will enhance the focus of the article.

1. The first sentence of the article, where the authors state that "Asthma is the most severe inflammatory disorder of the lung" is, I think, rather debatable. It should be rewritten in a less pretentious way.
   Answer: Thank you for the comments. We have revised the sentence to "Asthma is a common and heterogeneous disease characterized by chronic airway inflammation." **(Page 1, line 18-19)**

2. In both the abstract and the introduction, the authors state that "Currently, the two main types of asthma medicines are inhaled corticosteroids and long-acting β2-adrenoceptor agonists (LABAs)", however, the authors do not include the third major group which is constituted by biologic drugs (specifically monoclonal antibodies) against different targets.
   Answer: We sincerely thank the reviewer's comments and suggestions. We have revised the manuscript according to the reviewer's comments. There are currently two main types of asthma medicines, inhaled corticosteroids and long-acting β_2-adrenoceptor agonists (LABAs). In addition, biologic drugs provide another therapeutic option especially for the patients with severe asthma **(Abstract page 1, line 20-21)**. Severe asthma patients need add-on therapies, such as biological drugs (Monoclonal antibodies) that target specific molecular pathways **(Introduction page 2, line 62-64)**.

3. At no point in the introduction or the article do the authors cite the GINA (The Global Initiative for Asthma) Guidelines or Reports. Their latest edition of 2021 should be cited and included in the article, mentioning also the different phenotypes within the asthmatic disease.
   Answer: We thank you for the reviewer suggestions. We have mentioned the clinical phenotype of Asthma and cited the GINA 2021 in the introduction: "Asthma, a heterogeneous disease, is classified into different clinical phenotypes such as allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity." **(Page 1, line 40-43)**

4. Section "2.4 Statistical analysis" should be updated. The authors indicate only the programs used, but do not describe the statistical methods used in the work.
   Answer: Thanks for the reviewer comments. In this study, all analytic workflows were performed on RStudio version 4.0.3. We have added the citations for each program. Missense and Cis-expression quantitative trait locus (*Cis*-eQTL) were performed in R using the haploR package (Zhbannikov, I.Y et al., 2021). Over-representation analysis (ORA), including Knockout Mouse Phenotype, PPI network, and Molecular Pathway were performed using the WebGestalt R package (Wang, J. et al., 2020**) (Page 4, line 141-145).**

5. Table 1 represents a result of the authors' research and should therefore be included in this section and not in the discussion.

Answer: We are very grateful for the reviewer's suggestion. We have moved Table 1 to the result section as suggested by the reviewer **(Page 7-8, line 196-197).**

6. The discussion could be more elaborated, taking into account the different asthma phenotypes. A critical discussion of previous failures should also be included: for example, a critical reference should be made to other drugs that have not been successful in the treatment of Asthma after repositioning, as was recently the case with Risankizumab in Severe Asthma: N Engl J Med 2021; 385:1669-1679. DOI: 10.1056/NEJMoa2030880.
Answer: We sincerely thank you for your valuable suggestions. The last paragraph of the discussion were largely revised as follows:

Drug repurposing offers various advantages over developing an entirely new drug for a given indication, such as fewer risks, lower cost, and shorter development time (Fetro C et al., 2020). Nevertheless, this approach does not always succeed, one example was a recent case of risankizumab in severe Asthma. A phase 2a, placebo-controlled trial (NCT02443298) showed the repurposed drug might not benefit severe asthma patients (Christopher EB et al., 2021). The failure may be due to biological variations of biomarkers, etiology of disease and clinical phenotypes among patients. The deviations lead to different patterns of treatment response. In this study, we included previous reports of any types of asthma (e.g., chronic obstructive asthma, adult-onset asthma, atopic asthma, childhood-onset asthma), and extracted the asthma-associate genetic variants from GWAS and PheWAS catalogs. Without the further specification of patient subgroups, studies on animal models with different phenotypes and clinical trials are necessary to validate the effectiveness of the candidate drugs in practical usage. This study utilized incorporated genetic data, computational methods, and publicly accessible big data sets to prioritize the best candidate genes and identify new drugs for asthma therapy. However, there are some limitations. First, genes from the GWAS and PheWAS catalog's is not always druggable, and not all gene targets emerge distinct pharmacological activity. Our analysis showed that among 139 biological asthma risk genes, however, only 22 genes are druggable. Second, the therapeutic drugs found in this pipeline have not been validated. Further functional studies and clinical studies are required to determine the possibility of clinical application and implementation of our findings. **(Page 9-10, line 283-304)**.

7. In the discussion, the last sentence "In sum, the anti-IL6R (Sarilumab and Satralizumab) therapy could become novel asthma treatment options" should be rewritten. The authors should lower the expectations of their proposal given that neither further in vitro experiments nor experiments in animal models have been carried out.
Answer: We appreciate the reviewer's reminder. This sentence has been rewritten as follows. In summary, our results reveal that the anti-IL6R (Sarilumab and satralizumab) are promising candidates for drug repositioning to asthma therapy. However more studies from animal models and clinical trials will be helpful to carry out the mechanisms of anti-IL6R in asthma. **(Page 10, line 358-360)**.

8. The bibliography should be updated as there is not a single citation of articles published in 2021, and at least include the two named in this revision.
Answer: Thank you for the suggestions. We have added two reference articles published in 2021 (references 3 and 52).

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available online: https://ginasthma.org/.
2. Zhbannikov, I.Y.; Arbeev, K.; Yashin, A.I. Package ‘ haploR ’ Available online: https://cran.r-project.org/web/packages/haploR/index.html.
3. Wang, J.; Liao, Y.; Jaehnig, E.; Shi, Z.; Sheng, Q. Package ‘ WebGestaltR ’ Available online: https://cran.r-project.org/web/packages/WebGestaltR/index.html.
4. Fetro, C.; Scherman, D. Drug repurposing in rare diseases : Myths and reality. Therapies 2020, 75, 157–160, doi:10.1016/j.therap.2020.02.006.
5. E, C.; Brightling; Nair, P.; Cousins, D.J.; Louis, R.; Singh, D. Risankizumab in Severe Asthma — A Phase 2a, Placebo-Controlled Trial. N. Engl. J. Med. 2021, 385, 1669–1679, doi:10.1056/NEJMoa2030880.

Komentar reviewer 1 tahap 2:

Review Report Form

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	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	(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

Dear Authors,

I have read the revised manuscript and your comments and I can inform you that I have not comments

best regards

Luca

Submission Date 01 December 2021

Date of this review 23 Dec 2021 00:18:41

Komentar reviewer 3 tahap 2:

Review Report Form

Quality of English Language

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( ) I am not qualified to assess the quality of English in this paper

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Does the introduction provide sufficient background and include all relevant references?	(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)	( )	( )	( )

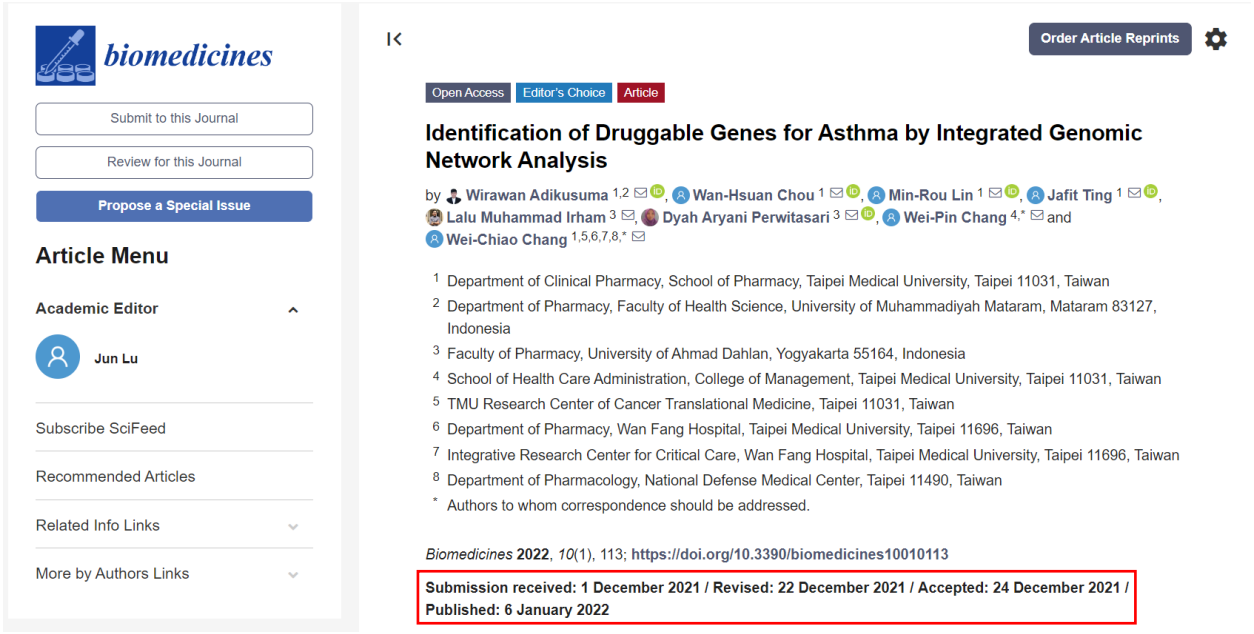
Comments and Suggestions for Authors

Thanks to the authors for their efforts. They have amended all the points I had previously indicated, so I think the article has been substantially improved.

Submission Date 01 December 2021

Date of this review 23 Dec 2021 12:32:16

Artikel accepted 24 desember 2021 dan terbit pada tanggal 6 januari 2022



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Identification of Druggable Genes for Asthma by Integrated Genomic Network Analysis

by Wirawan Adikusuma [1,2], Wan-Hsuan Chou [1], Min-Rou Lin [1], Jafit Ting [1], Lalu Muhammad Irham [3], Dyah Aryani Perwitasari [3], Wei-Pin Chang [4,*] and Wei-Chiao Chang [1,5,6,7,8,*]

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6 Department of Pharmacy, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan
7 Integrative Research Center for Critical Care, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan
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* Authors to whom correspondence should be addressed.

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