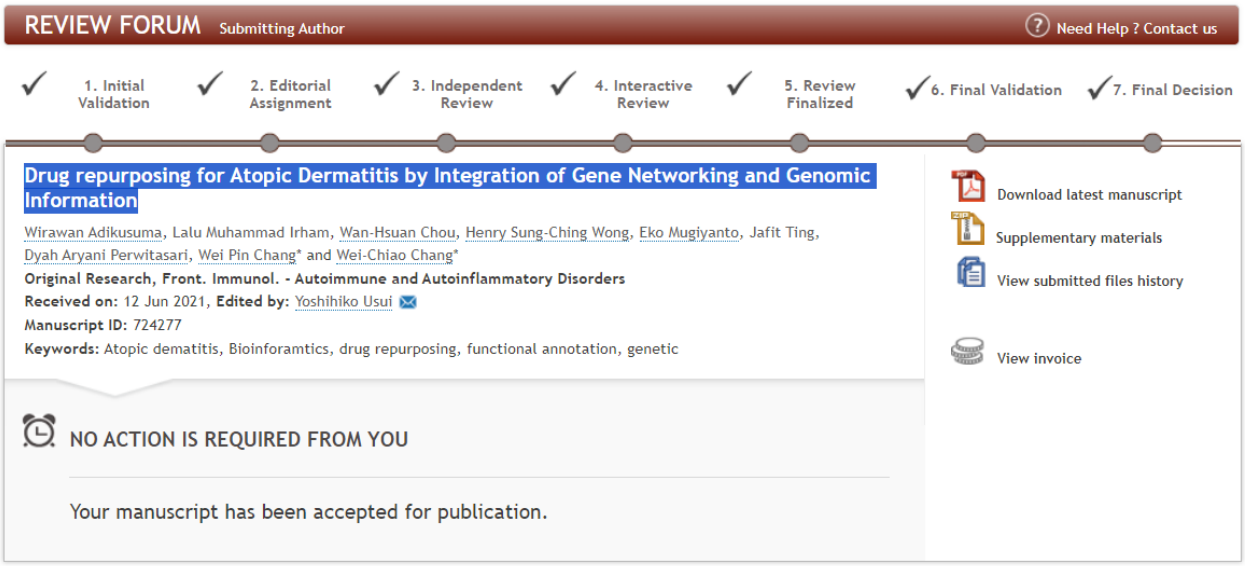
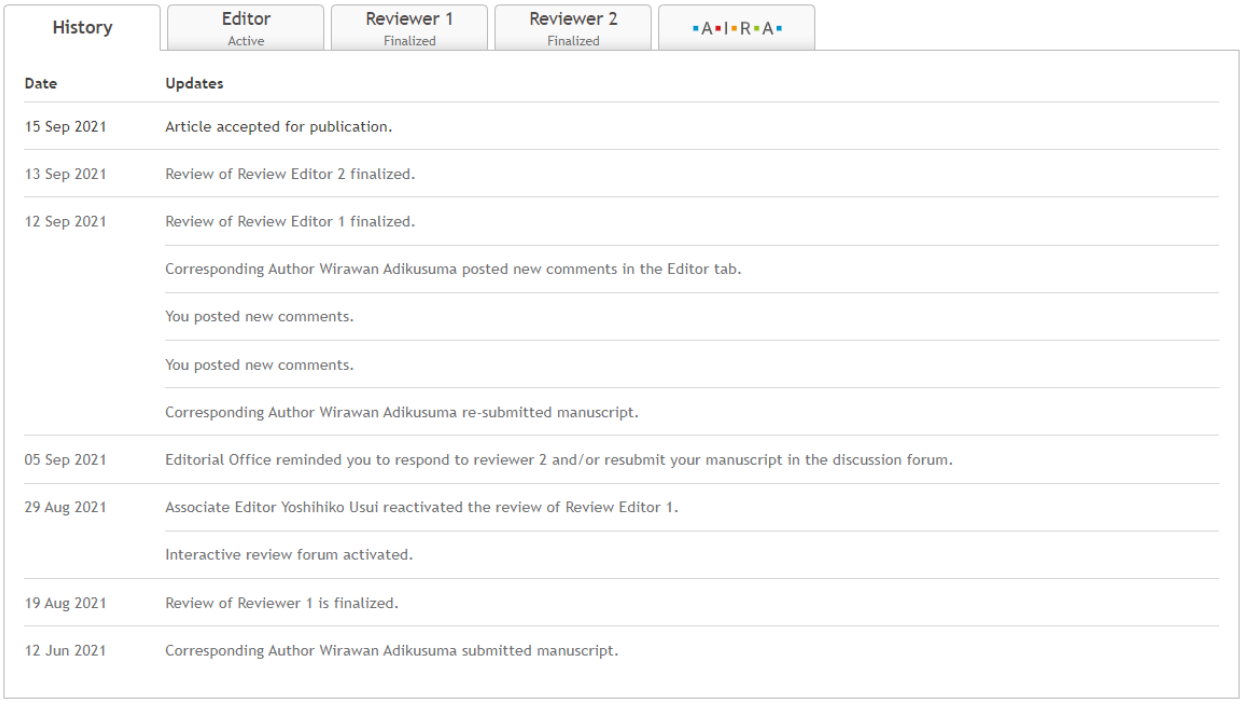
History Artikel

Drug repurposing for Atopic Dermatitis by Integration of Gene Networking and Genomic Information





Komentar reviewer 1:

History | Editor Active | Reviewer 1 Finalized | Reviewer 2 Finalized | ▪A▪I▪R▪A▪

Reviewer 1
Independent review report submitted: 19 Aug 2021
Interactive review activated: 29 Aug 2021
Final report submitted: 12 Sep 2021

Initial recommendation to the Editor: Accept in current form

Final Evaluation

Q 1 **Final comments to Author (optional):**

No answer given.

Q 2 **Do you ENDORSE THE PUBLICATION of this manuscript in its current form?**

Reviewer 1 | 12 Sep 2021 | 13:04

– Yes

EVALUATION

Q 1 **Please summarize the main findings of the study.**

Reviewer 1 | 19 Aug 2021 | 03:07 #1

In this study authors have identified that 27 AD risk genes were mapped into 76 known gene targets, and they discovered that 25 drug target genes were overlapping with 53 drugs. Among 53 drugs drugs, dupilumab is one of the 53 drugs successfully identified which is known for AD treatment. Based on their validated experimental set up, authors identified filgotinib and fedratinib which target JAK1 gene. These two drugs could be potential drugs for AD.

Corresponding Author: Wirawan Adikusuma | 12 Sep 2021 | 08:17 #2

We thanks for reviewer comments

Q 2 **Please highlight the limitations and strengths.**

Reviewer 1 | 19 Aug 2021 | 03:07 #1

See Q5

Q 3 **Please comment on the methods, results and data interpretation. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

Reviewer 1 | 19 Aug 2021 | 03:07 #1

See Q2

Q 4 **Check List**

Reviewer 1 | 19 Aug 2021 | 03:07 #1

Is the English language of sufficient quality?
- Yes

Is the quality of the figures and tables satisfactory?
- No

Does the reference list cover the relevant literature adequately and in an unbiased manner?
- Yes

Are the statistical methods valid and correctly applied? (e.g. sample size, choice of test)
- Yes

Are the methods sufficiently documented to allow replication studies?
- Yes

Are the data underlying the study available in either the article, supplement, or deposited in a repository? (Sequence/expression data, protein/molecule characterizations, annotations, and taxonomy data are required to be deposited in public repositories prior to publication)
- Yes

Does the study adhere to ethical standards including ethics committee approval and consent procedure?
- Not Applicable

Have standard biosecurity and institutional safety procedures been adhered to?
- Not Applicable

Q 5 **Please provide your detailed review report to the editor and authors (including any comments on the Q4 Check List):**

Reviewer 1 | 19 Aug 2021 | 03:07 #1

This manuscript describes drug repurposing for atopic dermatitis (AD) through gene networking and genomic information.

In this study authors have identified that 27 AD risk genes were mapped into 76 known gene targets, and they discovered that 25 drug target genes were overlapping with 53 drugs. Among 53 drugs drugs, dupilumab is one of the 53 drugs successfully identified which is known for AD treatment. Based on their validated experimental set up, authors identified filgotinib and fedratinib which target JAK1 gene. These two drugs could be potential drugs for AD.

This is very exciting study and successful validation on AD, their model could be useful for other diseases also.

Komentar reviewer 2

History | Editor Active | Reviewer 1 Finalized | Reviewer 2 Finalized | ▪A▪I▪R▪A▪

Reviewer 2
Independent review report submitted: 22 Jul 2021
Interactive review activated: 29 Aug 2021
Final report submitted: 13 Sep 2021

Initial recommendation to the Editor: Minor revision is required

Final Evaluation

Q 1 **Final comments to Author (optional):**

No answer given.

Q 2 **Do you ENDORSE THE PUBLICATION of this manuscript in its current form?**

Reviewer 2 | 13 Sep 2021 | 07:35

– Yes

EVALUATION

Q 1 **Please summarize the main findings of the study.**

Reviewer 2 | 22 Jul 2021 | 08:48 #1

In the present manuscript the authors have used an informatics strategy to identify atopic dermatitis (AD) druggable molecular targets. In particular, candidate gene from GWAS identified loci associated to AD were prioritized using in silico pipelines and building a scoring system that used six functional annotations to predict drug candidates.

Corresponding Author: Wirawan Adikusuma | 12 Sep 2021 | 07:46 #2

Thanks for the reviewer comments

Q 2 **Please highlight the limitations and strengths.**

Reviewer 2 | 22 Jul 2021 | 08:48 #1

Strength
1. The strategy of identification of druggable targets is clearly described and rigorously documented.
Limitation
1. Purely informatics approach with no "in house" demonstration of the validity of the less predictable new targets

Corresponding Author: Wirawan Adikusuma | 12 Sep 2021 | 07:46 #2

thanks for the reviewer comments

Q 3 **Please comment on the methods, results and data interpretation. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

No answer given.

Q 4 **Check List**

Reviewer 2 | 22 Jul 2021 | 08:48 #1

Is the English language of sufficient quality?
- Yes

Is the quality of the figures and tables satisfactory?
- Yes

Does the reference list cover the relevant literature adequately and in an unbiased manner?
- Yes

Are the statistical methods valid and correctly applied? (e.g. sample size, choice of test)
- Yes

Are the methods sufficiently documented to allow replication studies?
- Yes

Are the data underlying the study available in either the article, supplement, or deposited in a repository? (Sequence/expression data, protein/molecule characterizations, annotations, and taxonomy data are required to be deposited in public repositories prior to publication)
- Not Applicable

Does the study adhere to ethical standards including ethics committee approval and consent procedure?
- Not Applicable

Have standard biosecurity and institutional safety procedures been adhered to?
- Not Applicable

Q 5 **Please provide your detailed review report to the editor and authors (including any comments on the Q4 Check List):**

Reviewer 2 | 22 Jul 2021 | 08:48 #1

This is a well written and overall clear manuscript.
I have two major points that need clarification.
1. Fig 3. Here IL1R1 and IL18R1, identified by GWAS are linked to IL4R by PPI. It is unclear to me how this was achieved. I have doubts that a direct protein-protein interaction exist between IL4R and the other two. The STRNG data analysis does not report such an association. Please, clarify.
2. Among the identified drugs are mentioned foreskin keratinocytes. It would be important to discuss the pharmacological links between keratinocytes and the genes with whom they make associations in the perspective of therapies. If you consider them as biological drugs, you should state it and explain it. If you consider them as inappropriately found biological drugs, you should comment it.
Minor point.
1. Line 93: for the non experts, it will be important to explain what is included and excluded in the r2≥0.8 criterion

Merespon terhadap saran dan masukan dari para reviewer:

September 12, 2021

Dear Editors,

We appreciate this opportunity to submit our revised manuscript: "**Drug repositioning for atopic dermatitis by integration of gene networking and genomic information**" which we are submitting for consideration for publication as Original Research article in "***Frontiers in Immunology"* (Manuscript ID: 724277)**. We would like to thank the reviewer 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 2 comments: I have two major points that need clarification.

1. Fig 3. Here IL1R1 and IL18R1, identified by GWAS are linked to IL4R by PPI. It is unclear to me how this was achieved. I have doubts that a direct protein-protein interaction exist between IL4R and the other two. The STRNG data analysis does not report such an association. Please, clarify.

   Answer: We thank you for the reviewer comments. To address the reviewer's concern regarding IL1R1 and IL18R1 are linked to IL4R, we added the following statements.

   In the present study, we found 27 biological AD risk genes, including IL1R1 and IL18R1. The AD biological risk genes were expanded using the STRING database and set the criterion of 50 interactions to obtain more candidate drug target genes. This study obtained 76 genes as the drug target genes through the STRING database (supplementary table 4). STRING is a database of known and predicted protein-protein interactions. The interactions involve direct (physical) and indirect (functional) associations [1]. From this analysis, we obtained 2053 interaction pairs with 76 drug target genes involved from the curated PPI networking (Supplementary Table 5). As shown in Supplementary Table 5, four genes (IL10, IL6, IL1R1, and IL18R1) are linked to IL4R. In this point, we highlighted that two genes (IL1R1 and IL18R1) as part of biological risk genes directly linked to IL4R.

   Reference:

   N.T. Doncheva, J.H. Morris, P. Bork, L.J. Jensen, C. Von Mering, STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, Nucleic Acids Res. 47 (2019) D607–D613. https://doi.org/10.1093/nar/gky1131.

2. Among the identified drugs are mentioned foreskin keratinocytes. It would be important to discuss the pharmacological links between keratinocytes and the genes with whom they make associations in the perspective of therapies. If you consider them as biological drugs, you should state it and explain it. If you consider them as inappropriately found biological drugs, you should comment it.

   Answer: We thank you for the reviewer's comment and suggestions. To address the reviewer concern regarding foreskin keratinocytes, we have added the following statements in "Discussion" (page 9, lines 239 – 249). **This is a very important point. This study identified 27 biological AD risk genes and mapped them to 76 drug target genes. Among them, only 25 drug target genes are druggable that are able to link to 53 drugs. In this study, foreskin keratinocyte was linked to *EGFR*, *IL6*, and *IL1B*, as shown in Figure 5. Foreskin keratinocyte is a type of skin cell that is cultured as a wound skin cell replacement to speed up wound healing and closure. Foreskin keratinocytes are a key component of a number of skin replacements utilized for various indications [1]. Keratinocytes are generated from neonatal foreskins and utilized to make a drug called Apligraf, which is a mix of neonatal foreskin fibroblasts and keratinocytes. Orcel is another skin substitute that combines fibroblasts and keratinocytes produced from the neonatal foreskin, similar to Apligraf [2]. The**

epidermal growth factor receptor (*EGFR*) is a well-known regulator of a variety of epidermal functions. *EGFR* signaling is involved in keratinocytes differentiation and has contributes to the pathogenesis of multiple skin diseases, including AD. *EGFR* activation by *EGF* was found to protect against AD by decreasing IL-17A and IL-6 expression in an AD model that further demonstrated a protective role of EGF in the inflamed skin tissue [3]. Foreskin keratinocyte is an agonist for *EGFR*, however, more preclinical and clinical studies in AD models and patients are needed to demonstrate the efficacy of the drugs identified.

References:

[1] D. Szklarczyk, A.L. Gable, D. Lyon, A. Junge, S. Wyder, J. Huerta-Cepas, M. Simonovic, [2] B. ter Horst, G. Chouhan, N.S. Moiemen, L.M. Grover, Advances in keratinocyte delivery in burn wound care, Adv. Drug Deliv. Rev. 123 (2018) 18–32. https://doi.org/10.1016/j.addr.2017.06.012.

[2] M. Varkey, J. Ding, E. Tredget, Advances in Skin Substitutes—Potential of Tissue Engineered Skin for Facilitating Anti-Fibrotic Healing, J. Funct. Biomater. 6 (2015) 547–563. https://doi.org/10.3390/jfb6030547.

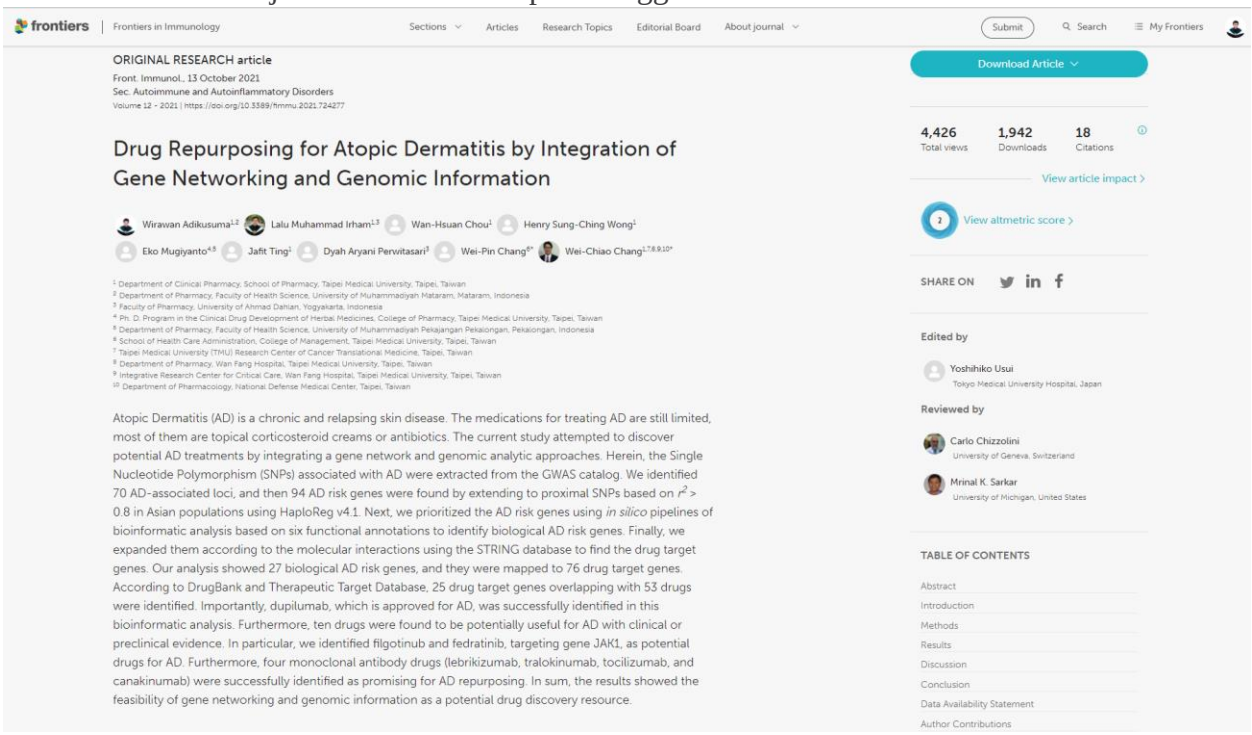
[3] Z. Zhang, C. Xiao, A.M. Gibson, S.A. Bass, G.K. Khurana Hershey, EGFR Signaling Blunts Allergen-Induced IL-6 Production and Th17 Responses in the Skin and Attenuates Development and Relapse of Atopic Dermatitis, J. Immunol. 192 (2014) 859–866. https://doi.org/10.4049/jimmunol.1301062.

Minor point.

1. Line 93: for the non experts, it will be important to explain what is included and excluded in the r2≥0.8 criterion.

   Answer: We thank you for the reviewer suggestions. The following statements have been added to "Methods" (Page 4, lines 95-99) according to the reviewer's suggestions**. The SNPs proxy to the AD risk SNPs were included based on Linkage Disequilibrium (LD) 's characteristic to define the AD risk SNPs. It was conducted using HaploReg (v4.1) [2] with the criterion of r2 ≥ 0.8 in Asian (ASN) populations from the 1000 Genome Project Phase I data. The AD risk SNPs were classified based on missense (or nonsense), synonymous or non-coding (with or without cis-eQTL) SNPs.**

Artikel di submit 12 juni 2021 dan terbit pada tanggal 13 oktober 2021



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Front. Immunol., 13 October 2021

Sec. Autoimmune and Autoinflammatory Disorders

Volume 12 - 2021 | https://doi.org/10.3389/fimmu.2021.724277

Drug Repurposing for Atopic Dermatitis by Integration of Gene Networking and Genomic Information

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Atopic Dermatitis (AD) is a chronic and relapsing skin disease. The medications for treating AD are still limited, most of them are topical corticosteroid creams or antibiotics. The current study attempted to discover potential AD treatments by integrating a gene network and genomic analytic approaches. Herein, the Single Nucleotide Polymorphism (SNPs) associated with AD were extracted from the GWAS catalog. We identified 70 AD-associated loci, and then 94 AD risk genes were found by extending to proximal SNPs based on $r^2 >$ 0.8 in Asian populations using HaploReg v4.1. Next, we prioritized the AD risk genes using *in silico* pipelines of bioinformatic analysis based on six functional annotations to identify biological AD risk genes. Finally, we expanded them according to the molecular interactions using the STRING database to find the drug target genes. Our analysis showed 27 biological AD risk genes, and they were mapped to 76 drug target genes. According to DrugBank and Therapeutic Target Database, 25 drug target genes overlapping with 53 drugs were identified. Importantly, dupilumab, which is approved for AD, was successfully identified in this bioinformatic analysis. Furthermore, ten drugs were found to be potentially useful for AD with clinical or preclinical evidence. In particular, we identified filgotinub and fedratinib, targeting gene JAK1, as potential drugs for AD. Furthermore, four monoclonal antibody drugs (lebrikizumab, tralokinumab, tocilizumab, and canakinumab) were successfully identified as promising for AD repurposing. In sum, the results showed the feasibility of gene networking and genomic information as a potential drug discovery resource.

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