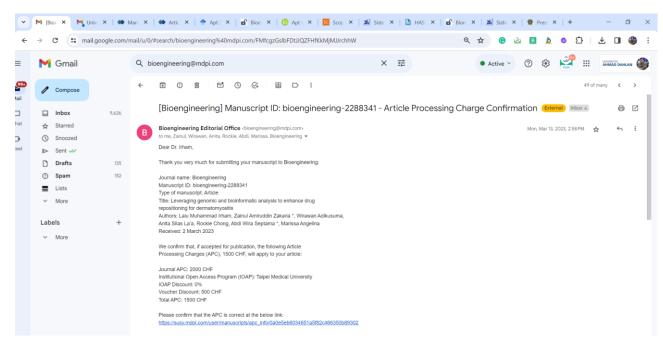
# Histori Artikel Berproses di Jurnal Bioengineering

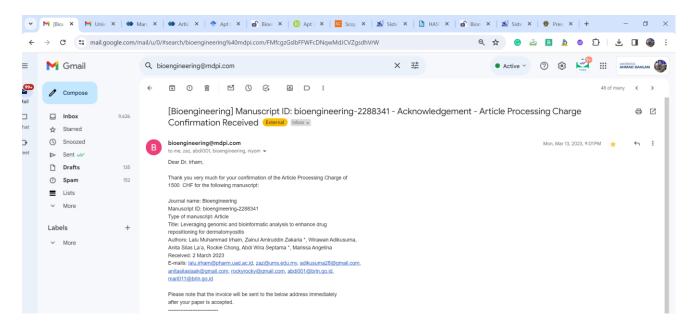
Journal	Bioengineering
Volume	Published: 27 Juni 2023. Bioengineering 2023, 10, 890.
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DOI	10.3390/bioengineering10080890
Authors	Lalu Muhammad Irham, Wirawan Adikusuma, Anita Silas La'ah, Rockie Chong, Abdi Wira Septama,* and Marissa Angelina
Title	Leveraging Genomic and Bioinformatic Analysis to Enhance Drug Repositioning for Dermatomyositis.
Link Artikel	https://www.mdpi.com/2306- 5354/10/8/890

Editorial process yang dilakukan penulis pada jurnal menggunakan sistem dari Publisher MDPI tersebut yang dapat di akses di alamat https://susy.mdpi.com/ dengan Informasi metadata artikel pada jurnal,sebagai berikut

Manuscript Submission (Mon, Mar 13, 2023, 2:58 PM)



Setelah disubmit melalui system MDPI, maka secara otomatis editor akan mengingatka Acknowledgment Submission kepada semua author yang dikirm melalui email dan dalam email tersebut juga editor mengingatkan terkait dengan pembiayaan jurnal jika nanti setelah dilakukan proses revisi dinyatakan ACCEPTED. kesediaan membayar APC jika di accepted (Mon, Mar 13, 2023, 9:01 PM)



#### Manuscript Submission ()

Editorial dari Bioengineering menkonfirmasi terkait dengan form kontribusi dari masing-masing author pada tanggal Mar 9, 2023, 4:30 PM

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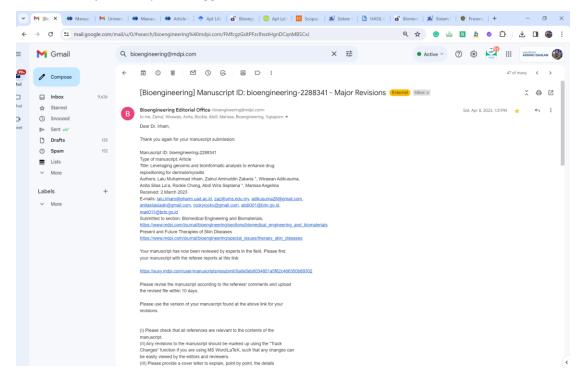
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Setelah menunggu sekian lama, kami mendapatkan informasi terkait dengan status artikal yang telah disubmit pada tanggal 13 Maret 2023. Pada tanggal 8 April 2023 kami mendapatkan kabar bahwa artikel yang kami submit dinyatakan MAJOR REVISION.

Informasi Major revisi pada tanggal Sat, Apr 8, 2023, 1:31 PM



Komentar dari DUA REVIEWER jurnal dapat dilihat pada penjelasan poin per poin dibawah ini:

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Word Count	4102	
Page Count	11	
Figure Count	3	
Table Count	3	
Reference Count	39	
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Decision	Accept in current form	
Decision Date	18 April 2023	
Review Report		
Reviewer 1	Review Report (Round 1)	
Reviewer 2	Review Report (Round 1)	
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Invoice ID	bloengineering-2288341_part1	
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		Comments and Suggestions for Authors	Authors described a novel approach for drug repositioning for dermatomyositis.	
			Major comments:	
			Regarding "Functional annotation of risk genes" - What was the rationale of oriteria selection? E.g. Why do the Authors focus on missense but not in the LoF variants category? Why do they not use any other criteria of pathogenicity, like MAF in reference databases, prediction scores etc? It is completely unclear how the "STRING database (https://string-db.org) was utilized to expand	
			the biological dermatomyositis risk genes" and how Authors can justify this expansion?	
			Minor comments: The number of genes with missense mutations (n=5) is different from the number of genes with missense mutations in Table 1.	
			"Interestingly, we found 44 genes with a score of 0 and 25 genes with a score of 1. Among <b>these</b> genes, 7 had a score of 2, and 3 had a total score of 3." <- I do not understand the second sentence. Among which genes?	
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			*Among the 43 new drug candidates, nine of which are currently undergoing clinical trials for dermatomyositis according to ClinicalTrial.gov (https://clinicaltrials.gov/), the candidate drugs are Triadcinib(NCT03002649), Banicithib (NCT05301109), Human immunoglobulin G	
			NCT02728752), Antithymocyte immunoglobulin (NCT00010335), Interferon alpha-n1 (NCT00533091), and Human interferon beta (NCT05152200). Six drug candidates are linked to as idemnistromystelli biological risk genes, including JAK1, JAK2, IFNAR1, FICRAR1, FICRAR3, SCIRA8,	
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**Open Review** 

Quality of English Language

- (x) I would not like to sign my review report
- ( ) I would like to sign my review report
- () English very difficult to understand/incomprehensible
- () Extensive editing of English language and style required
- (x) Moderate English changes required
- () 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

Authors described a novel approach for drug repositioning for dermatomyositis.

Major comments:

Regarding "Functional annotation of risk genes" - What was the rationale of criteria selection? E.g. Why do the Authors focus on missense but not in the LoF variants category? Why do they not use any other criteria of pathogenicity, like MAF in reference databases, prediction scores etc?

It is completely unclear how the "STRING database (https://string-db.org/) was utilized to expand the biological dermatomyositis risk genes" and how Authors can justify this expansion?

Minor comments:

The number of genes with missense mutations (n=5) is different from the number of genes with missense mutations in Table 1.

"Interestingly, we found 44 genes with a score of 0 and 25 genes with a score of 1. Among **these** genes, 7 had a score of 2, and 3 had a total score of 3." <- I do not understand the second sentence. Among which genes?

"We also dictated 10 genes with a score of more than 2 which were defined as "biological dermatomyositis risk genes" (Figure 1D). " – I can only see 3 genes, not 10 with a score more than 2. Should it be "score of more than 1"?

"Among the 43 new drug candidates, nine of which are currently undergoing clinical trials for dermatomyositis according to ClinicalTrial.gov (https://clinicaltrials.gov/), the candidate drugs are Tofacitinib(NCT03002649), Baricitinib (NCT05361109), Human immunoglobulin G (NCT02728752), Antithymocyte immunoglobulin (NCT00010335), Interferon alpha-n1 (NCT00533091), and Human interferon beta (NCT05192200). Six drug candidates are linked to six dermatomyositis biological risk genes, including JAK1, JAK2, IFNAR1, IFNAR2, FCGR3B, and CD4 (Figure 3). "

This is also confusing. First Authors mention about 9 drugs under clinical trials and than they list 6 genes related to 6 genes - how these were selected ?

I think that data from Figure 3 and 4 would be easier to follow if presented in the form of Table.

Submission Date

02 March 2023

23 Mar 2023 18:10:15

Date of this review

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	It is a well-presented and	d well-conducted	study.						
	I do have some commen	nts and suggestio	ns:						~
	1. What s the role of the	identified genes	in inflammat	ion and skin function? Authors	can use				
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	could be very helpful as								
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( ) English very difficult to understand/incomprehensible

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() 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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Comments and Suggestions for Authors

I think this is a good manuscript that describes an original approach to dermatomyositis genetic mechanisms.

It is a well-presented and well-conducted study.

I do have some comments and suggestions:

1. What s the role of the identified genes in inflammation and skin function? Authors can use these papers PMID: 23515576, 25545474 to identify immune-related systemic genes that are specifically transcribed during the inflammation or are specific for different skin cells. I believe this could be very helpful as dermatomyositis combines skin and systemic muscular pathology.

2. I also suggest authors think or describe the transcribed genes in the context of some specific intracellular functions like autophagy or melanogenesis like in the publications PMID: 18514490, 21879234. Melanogenesis has an impact on inflammation and changes in pigmentation are relevant for dermatomyositis. Autophagy is a common process in complex diseases. These parts would improve the translational impact of the manuscript.

Submission Date

02 March 2023

#### 07 Apr 2023 17:20:42

Berikut adalah Respon kami selaku Author kepada ke dua reviewer:

Quality of English Language

Date of this review

## **Reviewer 1**

**Open Review** 

Quality of English Language

- (x) I would not like to sign my review report
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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)	( )	( )	( )
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

Authors described a novel approach for drug repositioning for dermatomyositis.

**Answer:** We sincerely thank the reviewer for taking the time to review our work, and have addressed the comments point-by-point. We have also utilized a proofreading service to improve the quality of the language for this manuscript.

Major comments:

**Q1: Reviewer #1:** Regarding "Functional annotation of risk genes" - What was the rationale of criteria selection? E.g. Why do the Authors focus on missense but not in the LoF variants category? Why do they not use any other criteria of pathogenicity, like MAF in reference databases, prediction scores etc?

**A1:** We thank you for your comment. In response to the reviewer's question, we would like to provide a more detailed explanation of the methodology used in our study.

What was the rationale of criteria selection?

For this study, based on prioritized SNPs from genome-wide association studies (GWAS) and phenome-wide association studies (PheWAS), we used seven strict functional bioinformatic annotations (missense/LoF mutations, expression quantitative trait loci (eQTLs), protein-protein interactions (PPIs), knockout mouse phenotypes, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, and primary immunodeficiency (PID) to further prioritize disease genes and identify drug targets for inhibitory drug repositioning. These

annotations have also been validated by Okada *et al*. to prioritize causal risks alleles for complex traits such as rheumatoid arthritis, as well as biological candidate genes for the prioritized risk loci. We found this approach relevant to the study of complex traits such as dermatomyositis. Therefore, our methodology utilized a similar approach as a standardized pipeline to identify drug targets for this devastating disease.

To address the reviewer's query, we added the following text to clarify the rationale:

"We mapped genetic variants to corresponding genes with missense/loss-of-function (LoF) mutations, as these non-synonymous changes in a single base substitution can have a significant impact on protein expression. We then used eQTLs, which are regions in the genome that are associated with changes in gene expression, to identify variants that could potentially cause changes in gene expression in the direction of the tissues involved in dermatomyositis (i.e., whole blood and skin). Furthermore, we utilized PPIs to understand the relationships between diseases and biological protein networks. If the genes involved in these networks are related to dermatomyositis pathogenesis, inhibiting their protein could be a potential drug repurposing strategy. We also applied knockout mouse phenotypes and KEGG pathways to identify the molecular pathways enriched on the dermatomyositis-associated gene list and the genes involved. Finally, we incorporated PID diseases, which are innate immune diseases that have been associated with dermatomyositis, to identify genes that play a causal role in the disease."[Lines 110-122]

Reference:

Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014;506(7488):376-381.

Q: Why do the Authors focus on missense but not in the LoF variants category?

A: Variants were annotated in order of priority of missense (or nonsense), synonymous, or non-coding mutations. True LoF mutations are generally rare, and in our experience, are a minor source of variations that lead to viable drug repurposing targets – thus our focus on missense mutations for this study. We revised the text in the manuscript to reflect our variant annotation criteria as follows:

"Variants were first annotated in order of priority of missense (or nonsense), synonymous, or non-coding mutations. In particular, we mapped genetic variants to corresponding genes with missense/loss-of-function (LoF) mutations, as these non-synonymous changes in a single base substitution can have a significant impact on protein expression." [Lines 108-112]

Q: Why do they not use any other criteria of pathogenicity, like MAF in reference databases, prediction scores etc?

Dermatomyositis is a rare genetic disorder affecting ~6 to 13 person per million persons in the population. As most disease variants for dermatomyositis are rare, we elect not to apply an allele frequency cutoff (e.g. MAF) to increase the number of variants screened and the power of our study. We believe our approach provides rich, disease-specific information compared to computational modelling approaches that generate more

general variant prediction (e.g. prediction scores). Thus, we chose the strict functional annotation criteria aforementioned for this study.

**Q2: Reviewer #1:** It is completely unclear how the "STRING database (https://string-db.org/) was utilized to expand the biological dermatomyositis risk genes" and how Authors can justify this expansion?

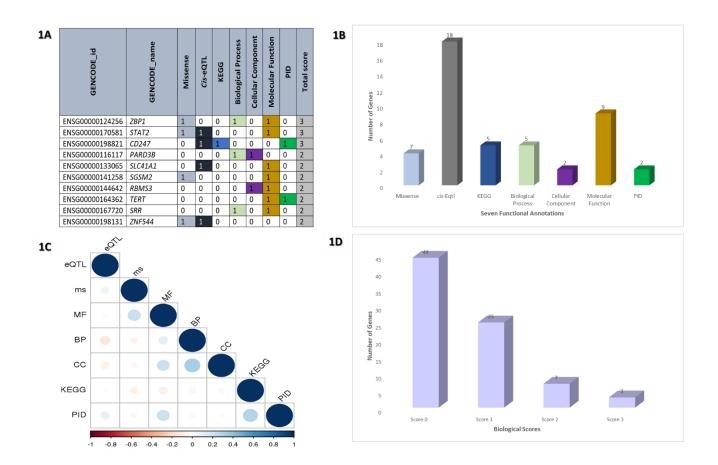
A2: Thank you for your valuable comment. We appreciate your feedback and have taken it into consideration. In our study, we used the STRING database to identify additional drug-targetable genes that may have a role in dermatomyositis pathogenesis. To identify the biological dermatomyositis risk genes, we applied a threshold of a biological score  $\geq 2$ . This allowed us to identify a larger number of genes that are potentially involved in dermatomyositis and may be candidates for drug repurposing. We found that increasing the threshold score resulted in a smaller number of genes being identified, which limits the number of potential drug targets we could observe. (i.e., we found 3 biological dermatomyositis genes for threshold score >=3, 7biological dermatomyositis genes for threshold score >=2, 25 biological dermatomyositis genes for threshold score >=1 [The number of genes with all biological scores can be found in **Table 1**]. Our study found that a higher number of biological dermatomyositis genes can lead to the identification of more candidate drug targets for dermatomyositis drug repurposing. However, we also observed that not all the identified drug target genes were druggable and only 13 out of 60 drug target genes were classified as "genetic driven druggable." This indicates that some of the identified drug targets may not be feasible targets for drug repurposing. We used a scoring system to assign one point for each functional annotation, and genes with a score  $\geq 2$  were classified as "biological dermatomyositis genes." We observed that the number of functional annotations ranged from 0-7 for the identified genes, and those genes with a higher score were more likely to be involved in dermatomyositis pathogenesis. In conclusion, we agree that the identification of druggable drug target genes is a crucial factor in drug repurposing for dermatomyositis. Our study aimed to identify a larger number of potential drug targets by using a threshold score of biological relevance. We acknowledge that not all the identified drug targets may be feasible for drug repurposing. We hope that our study provides valuable insights into the potential drug targets for dermatomyositis drug repurposing and will inspire further research in this area.

## Minor comments:

Q3: Reviewer #1: The number of genes with missense mutations (n=5) is different from the number of genes with missense mutations in Table 1.

A3: Thank you for bringing this to our attention. We apologize for any confusion that may have been caused. To clarify, we have carefully revised and verified the number of missense mutations in our study using **Table 1** and **Figure 1**. The total number of missense mutations in the identified genes is 7. We have updated the manuscript accordingly to reflect this correction. Thank you for helping us improve the accuracy and clarity of our work.





Q4: Reviewer #1: "Interestingly, we found 44 genes with a score of 0 and 25 genes with a score of 1. Among these genes, 7 had a score of 2, and 3 had a total score of 3." <- I do not understand the second sentence. Among which genes?

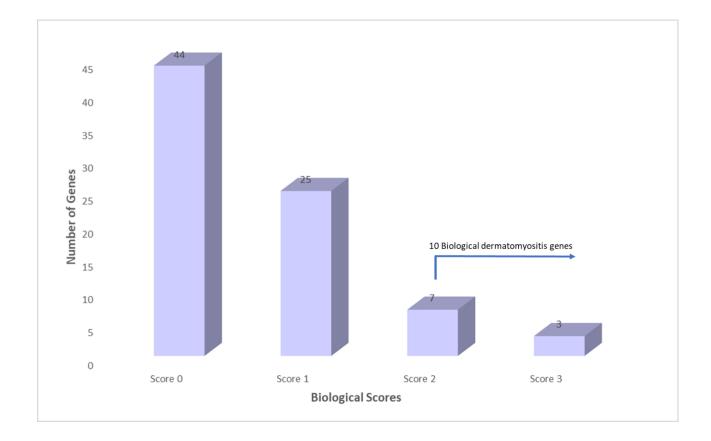
**A4:** Thank you for your valuable feedback. We have revised the sentences in question to provide more precise and scientific information. To clarify, the revised sentences are as below:

We found 44 genes with a score of 0, 25 biological DM genes for a threshold score  $\geq 1, 7$  biological DM genes for a threshold score  $\geq 2$ , and 3 genes with a threshold score  $\geq 3$ . To be considered biological risk genes, we required a score of more than 2 which were defined as "biological dermatomyositis risk genes" (Figure 1D) ". [Page 3, lines 128-132]. We hope that this revised information more clearly conveys our findings and conclusions. Thank you for helping us improve the clarity and accuracy of our manuscript.

**Q5: Reviewer #1:** "We also dictated 10 genes with a score of more than 2 which were defined as "biological dermatomyositis risk genes" (Figure 1D). "

- I can only see 3 genes, not 10 with a score more than 2. Should it be "score of more than 1"?

A5: We sincerely thank the reviewer for taking the time to review our work. According to the Figure 1D. Distribution of dermatomyositis-related gene scores. The figure, from left- to the right-side, showed number of genes with score  $0\sim3$ . Each gene was assigned one point for each functional annotation. Genes with a score of 0 have 44 genes. Genes with a score of 1 were 25 genes while those with a score of 2 were 7 genes and 7 genes with score of 3. After compiling the scores, 10 genes with a score of  $\geq2$ , which were categorized as 'biological dermatomyositis genes'.



**Q6: Reviewer #1:** "Among the 43 new drug candidates, nine of which are currently undergoing clinical trials for dermatomyositis according to ClinicalTrial.gov (https://clinicaltrials.gov/), the candidate drugs are Tofacitinib(NCT03002649), Baricitinib (NCT05361109), Human immunoglobulin G (NCT02728752), Antithymocyte immunoglobulin (NCT00010335), Interferon alpha-n1 (NCT00533091), and Human interferon beta (NCT05192200). Six drug candidates are linked to six dermatomyositis biological risk genes, including JAK1, JAK2, IFNAR1, IFNAR2, FCGR3B, and CD4 (Figure 3). "

A6: Thank you for your comment. We have revised the sentence as follows:

"Of these candidates, six are currently undergoing clinical trials according to ClinicalTrial.gov (https://clinicaltrials.gov/). These drug candidates are linked to six biological DM risk genes: JAK1, JAK2, IFNAR1, IFNAR2, FCGR3B, and CD4 (**Table 2**). In total, we identified nine unique combinations of drugs under clinical investigation for the six target genes (Table 2), corresponding to six unique drugs. The six drug candidates are tofacitinib (NCT03002649), baricitinib (NCT05361109), human immunoglobulin G (NCT02728752), antithymocyte immunoglobulin (NCT00010335), interferon alpha-n1 (NCT00533091), and human interferon beta (NCT05192200)." [lines 155 -161].

**Q7: Reviewer #1:** This is also confusing. First Authors mention about 9 drugs under clinical trials and than they list 6 genes related to 6 genes - how these were selected ?

A6: We apologize for the confusion. For **Table 2**, we refer to 9 total drugs under clinical investigation, which correspond to 6 *unique* for the 6 target genes. We added this to clarify in the text:

"Of these candidates, six are currently undergoing clinical trials according to ClinicalTrial.gov (https://clinicaltrials.gov/). These drug candidates are linked to six biological DM risk genes: JAK1, JAK2, IFNAR1, IFNAR2, FCGR3B, and CD4 (**Table 2**). In total, we identified nine unique combinations of drugs under clinical investigation for the six target genes (Table 2), corresponding to six unique drugs. The six drug candidates are tofacitinib (NCT03002649), baricitinib (NCT05361109), human immunoglobulin G (NCT02728752), antithymocyte immunoglobulin (NCT00010335), interferon alpha-n1 (NCT00533091), and human interferon beta (NCT05192200). [lines 155 -161].

**Q8: Reviewer #1:** I think that data from Figure 3 and 4 would be easier to follow if presented in the form of Table.

**A8:** Thank you for bringing this to our attention, and I appreciate your feedback in helping to improve the clarity of the presentation of the study's results. We have now provided the data in a table format as follows:

**NCT Number** Gene **Original Indication** Drug JAK2 Tofacitinib Severe Rheumatoid arthritis NCT03002649 JAK2 Baricitinib Severe Rheumatoid arthritis NCT05361109 FCGR3B Human immunoglobulin G Thrombocytopenic purpura NCT02728752 CD4 Antithymocyte immunoglobulin **Rejection Acute Renal** NCT00010335 IFNAR1 Interferon alfa-n1 Genital warts NCT00533091 IFNAR1 Human interferon beta **Multiple Sclerosis** NCT05192200

**Table 2**. Drugs under clinical investigation for DM, with identified drugs and their corresponding target genes.

JAK1	Tofacitinib	Rheumatoid arthritis	NCT03002649
JAK1	Baricitinib	Rheumatoid arthritis	NCT05361109
IFNAR2	Interferon alfa-n1	Genital warts	NCT00533091

**NCT Number**: The National Clinical Trial identifier number (ClinicalTrials.gov)

Table 3. Drugs under pre-clinical investigation and their correspondence with DM target genes

Gene	Target drug	PMID
JAK1, JAK2	Ruxolitinib	26448614
	Tofacitinib	33258553
	Upadacitinib	35081305
	Baricitinib	35318646
	Filgotinib	32222877
IFNAR1, IFNAR2	Human interferon beta	27564228
	Interferon alfa-2a	24638953
	Interferon beta-1a	18936398

PMID: PubMed identifier

**Open Review** 

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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)	( )	( )	( )
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Comments and Suggestions for Authors

I think this is a good manuscript that describes an original approach to dermatomyositis genetic mechanisms.

It is a well-presented and well-conducted study.

Answer: We sincerely thank the reviewer for taking the time to review our work, and have appreciating the importance and our approach for this study.

I do have some comments and suggestions:

**Q1: Reviewer #2:** What s the role of the identified genes in inflammation and skin function? Authors can use these papers PMID: 23515576, 25545474 to identify immune-related systemic genes that are specifically transcribed during the inflammation or are specific for different skin cells. I believe this could be very helpful as dermatomyositis combines skin and systemic muscular pathology.

**A1:** Thank you for your question. We appreciate the reviewer's suggestion and have taken it into account. The identified genes in our study are known to be associated with the biological risk of dermatomyositis based on GWAS and PheWAS catalogs, using seven functional annotation criteria to prioritize the genes and through gene network expansion to obtain candidate drug targets for dermatomyositis. While the specific role of these genes in inflammation and skin function is yet to be fully understood, we agree that investigating the expression of these genes in immune-related systemic genes that are specifically transcribed during inflammation or are specific for different skin cells could provide further insights into their potential roles in dermatomyositis. We have included these important studies in the discussion section (PMID: 23515576,

Quality of English Language

25545474), and will consider incorporating these suggestions in our future research. We have added sentence as follows [Lines 222-234]:

CD4 T lymphocytes plays an important role in the pathogenesis of DM by triggering antibodies that repair damaged vascular components [27]. We found that drugs that overlap with CD4 include human interferon beta, interferon alpha-2a, and interferon beta-1a. Meanwhile, IFNAR1 and IFNAR2 are IFN-α receptor subunits that affect DM. As IFNAR activates IFN-1, it causes muscle and endothelial cell damage, resulting in DM disease [28]. In addition, interferon beta is a drug that overlaps with IFNAR1 while interferon alpha-1 is a drug that overlaps with INFAR2. Thus, we also identified drugs overlapping with FCGR3B as Human Immunoglobulin G. According to the mechanism of drug action, this can block the Fc receptors by binding to the inhibitory receptors (FcgR2b) of Fc by activating FcgR1 and FcgR3 receptors, thereby suppressing the antibodies [29]. Of note, the expression of identified target genes that are immune-related systemic genes could be specifically transcribed during inflammation or are specific for different skin cells, and could provide further insights into their potential roles in dermatomyositis [30, 31]

**Q2: Reviewer #2:** I also suggest authors think or describe the transcribed genes in the context of some specific intracellular functions like autophagy or melanogenesis like in the publications PMID: 18514490, 21879234. Melanogenesis has an impact on inflammation and changes in pigmentation are relevant for dermatomyositis. Autophagy is a common process in complex diseases. These parts would improve the translational impact of the manuscript.

A2: Thank you for your insightful comment on our manuscript. We agree that incorporating the context of specific intracellular functions, such as autophagy or melanogenesis, could enhance the translational relevance of our findings. We have added sentence in the discussion part as follows [Lines 188 – 197]:

"Dermatomyositis is an autoimmune disease characterized by inflammatory features that affect the skin and muscles. Dysregulation of melanogenesis may contribute to the pathogenesis of dermatomyositis by affecting immune responses, such as antigen presentation, cytokine production, and T cell activation, which are modulated by melanin. Additionally, autophagy dysfunction has been linked to various autoimmune disorders, including dermatomyositis, as it is involved in maintaining cellular homeostasis and regulating protein quality control. In dermatomyositis, autophagy dysfunction can result in the accumulation of protein aggregates and impaired clearance of apoptotic cells, leading to the release of autoantigens and activation of the immune system [23] [24]. Therefore, targeting autophagy may be a potential therapeutic strategy for dermatomyositis." **[Lines 188 – 197].** 

Berikut adalah perubahan pada artikel yang telah kami buat sesuai dengan masukan dari para reviewer:

## (Research Article)

## Leveraging genomic and bioinformatic analysis to enhance drug repositioning for dermatomyositis

Lalu Muhammad Irham<sup>1,2,</sup>, Wirawan Adikusuma<sup>2</sup>, Anita Silas La'ah<sup>3</sup>, Rockie Chong<sup>4</sup>, Abdi Wira Septama<sup>5\*</sup>, Marissa Angelina<sup>5</sup>

**Citation:** To be added by editorial staff during production.

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Received: date Revised: date Accepted: date Published: date



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**Abstract:** Dermatomyositis (DM) is an autoimmune disease that is classified as a type of idiopathic inflammatory myopathy, which affects human skin and muscles. The most common clinical symptoms of DM are muscle weakness, rash, and scaly skin. There is currently no cure for DM. Genetic factors are known to play a pivotal role in DM progression, but few have utilized this information geared toward drug discovery for the disease. Here, we exploited genomic variation associated with DM and integrated this with genomic and bioinformatic analyses to discover new drug candidates. We first integrated GWAS and PheWAS catalogs to identify disease-associated genomic variants. Biological risk genes for DM were prioritized using strict functional annotations, further identifying candidate drug targets based on druggable genes from databases. Overall, we analyzed 1,239 variants associated with DM and obtained 43 drugs that overlapped with 13 target genes (*JAK2, FCGR3B, CD4, CD3D, LCK, CD2, CD3E, FCGR3A, CD3G, IFNAR1, CD247, JAK1, IFNAR2*). Six drugs clinically investigated for DM, as well as eight drugs under pre-clinical investigation, are candidate drugs that could be repositioned for DM. Further studies are necessary to validate potential biomarkers for novel DM therapeutics from our findings.

Keywords: Dermatomyositis, drug discovery, genomic variants, drug repositioning

#### 1. Introduction

Dermatomyositis (DM) is a rare disease that leads to chronic skin and muscle inflammation, classified as a type of Idiopathic Inflammatory Myopathy [1]. DM is highly prevalent in Asian populations [2, 3] and most common in women compared to men between the ages of 40 and 50 years [4]. The etiology of DM involves genetics, immunologic, and environmental factors [1]. For instance, DM has been genetically linked to patients with certain human leukocyte antigen (HLA) types [1]. Some haplotypes associated with high risk include *HLA-A\*68* in North American Whites [5], *HLA-DRB1\*0301* in African Americans [6], and *HLA-DQA1\*0104* and *HLA-DRB1\*07* in Han Chinese [7].

Several symptoms of DM include muscle weakness, myalgia, periungual telangiectasias, dystrophic cuticles, and a reddish rash on the heliotrope around the eyes [8]. In particular, a severe symptom of DM is dystrophic calcinosis, which is the deposition of calcium in the soft tissue of DM patients. This is a very painful condition that commonly affects children and adolescents but is rare in adults [9]. Calcinosis develops within 3 years of diagnosis due to delayed diagnosis, insufficient or resistance to treatment, long untreated duration, and severe disease course [9, 10]. Calcium channel blockers, especially non-dihydropyridine such as diltiazem, have been beneficial in managing calcinosis. Furthermore, prednisone, azathioprine, and methotrexate have often been used in DM patients [11]. Considering the severity of DM, these treatment approaches have been in use but there is still no cure for DM.

Extensive investigation has also been carried out towards improving DM. However, no proven drugs are currently available to halt the progression of DM. It is important to note that the discovery of new drugs is extremely costly, a high-risk, and a time-consuming process [12]. Considering the process of drug development, bringing a new drug to the market is estimated to take around 15 years with more than \$1 billion [13]. With that in mind, the concept of drug repurposing approaches offers a great opportunity to identify a new drug candidate in a shorter time frame, and with a lower cost in comparison with the complete discovery of a new drug candidate. In light of this, the use of drug repositioning has been known to enable the identification of new indications for existing drugs, and could be a promising strategy for intractable diseases such as DM.

Currently, genomic approaches are beginning to be widely adopted even for rare diseases, due to the availability of several genomic tools to identify genetic markers, resulting in disease prediction and drug discovery. Some genomic tools and databases include genome-wide association study (GWAS) and phenome-wide association study (PheWAS) catalogs. These databases are used to provide multiple risk loci for various diseases including DM. GWAS and PheWAS catalog databases are a rich source of genetic variants associated with disease such as DM. However, the clinical implementation that involves the translation of valuable biological insight into biological risk genes is limited.

In the present study, we integrated genomic variants involved in DM by using a strict bioinformatics approach. We also applied the functional annotation-driven biological insight based on molecular mechanisms and genetic linkage for DM. Finally, we identified a short list of potential candidate drugs to be repositioned for DM.

## 2. Results

First, we retrieved genomic variants associated with DM from GWAS and PheWAS catalogs. Secondly, we prioritized the DM risk genes prioritized based on seven strict functional annotations. Third, we applied network analysis for DM biological risk genes. Finally, a prioritized list of drugs is obtained for DM using drug databases.

#### 2.1 Variants associated with dermatomyositis from GWAS and PheWAS catalogs

The current study for DM focused on the application two widely genomic databases, including GWAS and PheWAS catalogs to identify functional genomic variants. We found three SNPs from GWAS catalog which were significantly associated with DM (odds ratio (OR) > 1 and *p*-value  $< 5x10^{-8}$ ) and 49 associated single nucleotide polymorphisms (SNPs) from PheWAS catalog (OR > 1 and *p*-value < 0.05). We further expanded the genomic variants based on the neighborhood with LD >0.8 to filter the same characteristic among variants. Finally, we identified 1,239 SNPs and found 78 genes that were encoded by the variants. We further prioritized the biological DM risk genes based on the filters from the scoring system.

#### 2.2 Functional annotation of dermatomyositis risk genes

Seven biological functional annotations were used to prioritize the biological risk genes for DM. One point is awarded for each functional annotation. Scores are assigned to each candidate gene using the following seven criteria: (1) gene variation with missense mutation (n = 5); (2) gene variations that have a risk for *cis* expression quantitative trait locus (*cis*-eQTL) (n = 18); (3) genes that overlap with Kyoto Encylopedia of Genes and Genomes (KEGG) (n = 5); (4) biological processes (n = 5); (5) cellular components (n = 2); (6) molecular functions (n = 9); (7) biological risk genes that overlap with Primary Immunodeficiency (PID) (n = 2) (**Table 1** and **Figure 1**). Variants were first annotated in

order of priority of missense (or nonsense), synonymous, or non-coding mutations. In particular, we mapped genetic variants to corresponding genes with missense/loss-offunction (LoF) mutations, as these non-synonymous changes in a single base substitution can have a significant impact on protein expression. We then used eQTLs, which are regions in the genome that are associated with changes in gene expression, to identify variants that could potentially cause changes in gene expression in the direction of the tissues involved in DM (i.e., whole blood and skin). Furthermore, we utilized PPIs to understand the relationships between diseases and biological protein networks. If the genes involved in these networks are related to DM pathogenesis, inhibiting their protein could be a potential drug repurposing strategy. We also applied knockout mouse phenotypes and KEGG pathways to identify the molecular pathways enriched on the DMassociated gene list and the genes involved. Finally, we incorporated PID diseases, which are innate immune diseases that have been associated with DM, to identify genes that play a causal role in the disease.

Next, we scored each gene based on the number of criteria met (scores from 0 to 7 for each gene) (Figure 1A and 1B). In order to avoid overlapping between functional annotations, a correlation coefficient analysis was performed. It is more likely that functional annotations will overlap if the value is close to one. Figure 1C depicts the result of the seven functional annotations with values between 0.2-0.6, indicating that not overlapping between each of functional annotation. We found 44 genes with a score of  $0_{\ell}$ 25 biological DM genes for threshold score  $\geq$  1, 7 biological DM genes for threshold score  $\geq$  2, and 3 genes with threshold score  $\geq$  3. To be considered biological risk genes, we required a score of more than 2 which were defined as "biological dermatomyositis risk genes" (Figure 1D). As shown in Table 1, 10 of the biological DM risk genes are Z-DNA Binding Protein 1 (ZBP1), Signal transducer and activator of transcription 2 (STAT2), Cluster of Differentiation 247 (CD247), Par-3 Family Cell Polarity Regulator Beta (PARD3B), Solute Carrier Family 41 Member 1 (SLC41A1), Small G Protein Signaling Modulator 2 (SGSM2), RNA Binding Motif Single Stranded Interacting Protein 3 (RBMS3), Telomerase Reverse Transcriptase (TERT), Serine Racemase (SRR), and Zinc Finger Protein 544 (ZNF544).

Table 1. Seven functional annotations were applied to prioritize the biological risk genes for dermatomyositis (DM).

GENCODE ID	Gene Name (GENCODE)	Missense	Cis-eQTL	KEGG	<b>Biological Process</b>	Cellular Component	Molecular Function	PID	Total score
ENSG00000124256	ZBP1	1	0	0	1	0	1	0	3
ENSG00000170581	STAT2	1	1	0	0	0	1	0	3
ENSG00000198821	CD247	0	1	1	0	0	0	1	3
ENSG00000116117	PARD3B	0	0	0	1	1	0	0	2
ENSG00000133065	SLC41A1	0	1	0	0	0	1	0	2
ENSG00000141258	SGSM2	1	0	0	0	0	1	0	2
ENSG00000144642	RBMS3	0	0	0	0	1	1	0	2
ENSG00000164362	TERT	0	0	0	0	0	1	1	2
ENSG00000167720	SRR	0	0	0	1	0	1	0	2
ENSG00000198131	ZNF544	1	1	0	0	0	0	0	2

ENSG0000069275	NUCKS1	0	1	0	0	0	0	0	1
ENSG0000069667	RORA	0	0	1	0	0	0	0	1
ENSG00000103653	СЅК	0	1	0	0	0	0	0	1
ENSG00000110944	IL23A	0	0	1	0	0	0	0	1
ENSG00000112294	ALDH5A1	0	1	0	0	0	0	0	1
ENSG00000117280	RAB7L1	0	1	0	0	0	0	0	1
ENSG00000128815	WDFY4	0	1	0	0	0	0	0	1
ENSG00000128915	NARG2	0	1	0	0	0	0	0	1
ENSG00000135469	COQ10A	1	0	0	0	0	0	0	1
ENSG00000135823	STX6	0	0	0	1	0	0	0	1
ENSG00000135903	PAX3	0	0	0	0	0	1	0	1
ENSG00000137261	KIAA0319	0	1	0	0	0	0	0	1
ENSG00000139540	SLC39A5	0	0	0	0	0	1	0	1
ENSG00000139645	ANKRD52	1	0	0	0	0	0	0	1
ENSG00000144785	RP11-977G19	0	1	0	0	0	0	0	1
ENSG00000152595	MEPE	0	0	0	1	0	0	0	1
ENSG00000160185	UBASH3A	0	1	0	0	0	0	0	1
ENSG00000183354	KIAA2026	0	1	0	0	0	0	0	1
ENSG00000204287	HLA-DRA	0	0	1	0	0	0	0	1
ENSG00000231389	HLA-DPA1	0	0	1	0	0	0	0	1
ENSG00000237241	RP11563N6.4	0	1	0	0	0	0	0	1
ENSG00000238809	snoU13	0	1	0	0	0	0	0	1
ENSG00000245534	RP11-219B17	0	1	0	0	0	0	0	1
ENSG00000259462	RP11-752G15	0	1	0	0	0	0	0	1
ENSG00000261801	RP11-941F15	1	0	0	0	0	0	0	1



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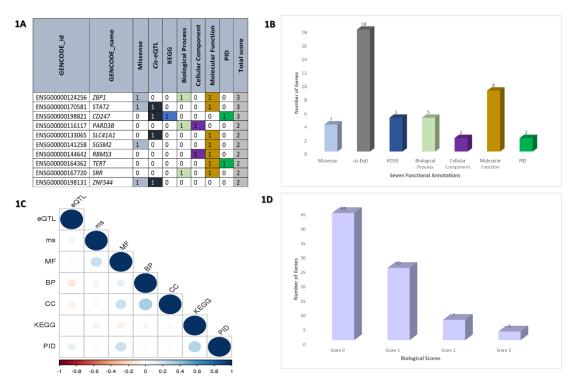


Figure 1. A. Functional bioinformatic annotations were integrated with genomic information 2 to prioritize dermatomyositis (DM) biological risk genes. B. Number of genes for each of the 3 seven biological criteria used for DM risk gene prioritization. C. Correlogram indicating the 4 pairwise Phi correlation coefficient across the seven criteria for DM risk gene prioritization. 5 Blue color denotes a positive correlation while red color denotes a negative correlation. D. 6 Distribution of scores based on the DM risk-gene annotations from the annotation scoring 7 system (0 to 3, with 3 being the highest score)., with the number of genes for each score bin 8 indicated. 9

#### 2.3 Gene network expansion through utilization of the STRING Database

Ten biological DM risk genes were developed by using STRING database (https://string-db.org/). Through this step using the STRING database we obtained 60 genes as target genes, which were used for further analysis.

#### 2.4 Prioritization of drugs repurposed for dermatomyositis

For this, we mapped 60 target genes into drug databases (DrugBank and DGIdb). We found 43 new drug candidates targeting 13 DM biological risk genes based on the mapping in drug databases (Figure 2). Of these candidates, six are currently undergoing clinical trials according to ClinicalTrial.gov (https://clinicaltrials.gov/). These drug candidates are linked to six biological DM risk genes: JAK1, JAK2, IFNAR1, IFNAR2, FCGR3B, and CD4 (**Table 2**). In total, we identified nine unique combinations of drugs under clinical investigation for the six target genes (Table 2), corresponding to six unique drugs. The six drug candidates are tofacitinib (NCT03002649), baricitinib (NCT05361109), human immunoglobulin G (NCT02728752), antithymocyte immunoglobulin (NCT00010335), interferon alpha-n1 (NCT00533091), and human interferon beta (NCT05192200). According to PubMed analysis (https://pubmed.ncbi.nlm.nih.gov/), among the 43 drug candidates, eight of the identified drugs are currently under preclinical testing for DM, including ruxolitinib [14], tofacitinib [15], upadacitinib [16], baricitinib [17], filgotinib [18], human interferon beta [19], interferon alfa-2a [20], and interferon beta-1[21] (Table 3). These eight drugs were associated with four DM risk genes, including JAK1, JAK2, IFNAR1, and IFNAR2.

In conclusion, we found 11 new drug candidates (tofacitinib, baricitinib, human immunoglobulin G, antithymocyte immunoglobulin, interferon alfa-n1, human interferon, ruxolitinib, upadacitinib, filgotinib, interferon alfa-2a, and interferon beta-1) for DM which supported both clinical and pre-clinical data. Furthermore, we observed that case reports suggesting that Janus kinase inhibitors [22] may be effective in DM, and the effect may be mediated by preventing the observed upregulation of type 1 interferon [12]. We also found 43 drugs that overlapped with 13 target genes (*JAK2, FCGR3B, CD4, CD3D, LCK, CD2, CD3E, FCGR3A, CD3G, IFNAR1, CD247, JAK1*, and *IFNAR2*). It is important to highlight that these targets not only can be useful as diagnostic biomarker and for prognosis, but can also drive drug target identification for DM. Finally, our findings revealed genomic variation as a powerful driver for drug repositioning for DM and can potentially be applied to other complex diseases.

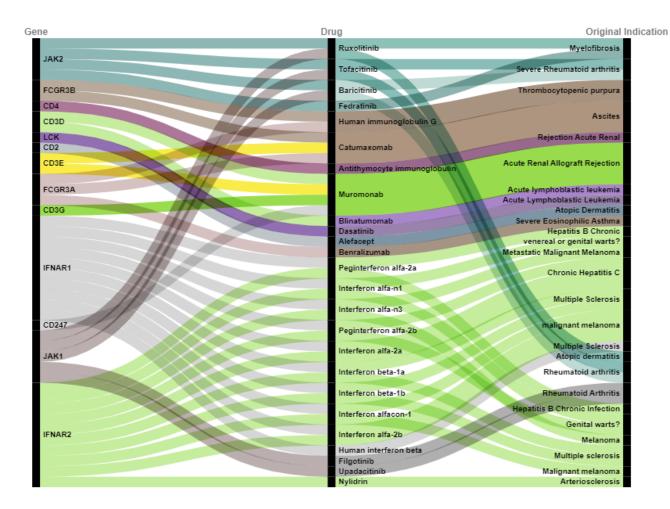


Figure 2: Alluvial diagram showing the 43 drugs overlapped with 13 target genes for DM

**Table 2**. Drugs under clinical investigation for DM, with identified drugs and their corresponding target genes for DM.

Gene	Drug	Original Indication	NCT Number
JAK2	Tofacitinib	Severe Rheumatoid arthritis	NCT03002649
JAK2	Baricitinib	Severe Rheumatoid arthritis	NCT05361109
FCGR3B	Human immunoglobulin G	Thrombocytopenic purpura	NCT02728752
CD4	Antithymocyte immunoglobulin	Rejection Acute Renal	NCT00010335
IFNAR1	Interferon alfa-n1	Genital warts	NCT00533091
IFNAR1	Human interferon beta	Multiple Sclerosis	NCT05192200
JAK1	Tofacitinib	Rheumatoid arthritis	NCT03002649
JAK1	Baricitinib	Rheumatoid arthritis	NCT05361109
IFNAR2	Interferon alfa-n1	Genital warts	NCT00533091

NCT Number: National Clinical Trial identifier number (ClinicalTrials.gov)

<b>Table 3.</b> Drugs under pre-clinical investigation and their correspondence with target	
genes for DM	

Target Gene	Drug	PMID
JAK1, JAK2	Ruxolitinib	26448614
	Tofacitinib	33258553
	Upadacitinib	35081305
	Baricitinib	35318646
	Filgotinib	32222877
IFNAR1, IFNAR2	Human interferon beta	27564228
	Interferon alfa-2a	24638953
	Interferon beta-1a	18936398
PMID: PubMed identifier		

#### 3. Discussion

Dermatomyositis (DM) is an autoimmune disease characterized by inflammatory features that affect the skin and muscles. Dysregulation of melanogenesis may contribute to the pathogenesis of DM by affecting immune responses, such as antigen presentation, cytokine production, and T-cell activation, which are modulated by melanin. Additionally, autophagy dysfunction has been linked to various autoimmune disorders, including DM, as it is involved in maintaining cellular homeostasis and regulating protein quality control. In DM, autophagy dysfunction can result in the accumulation of protein aggregates and impaired clearance of apoptotic cells, leading to the release of autoantigens and activation of the immune system[23] [24]. Therefore, targeting autophagy may be a potential therapeutic strategy for DM.

In this study, we used the genomic databases (GWAS and PheWAS catalogs) to obtain information on DM susceptibility genes and to further prioritize genes that are at risk for DM based on functional annotations. Herein, the use of genetic research to understand disease biology and its application in the clinic represents a useful approach for DM. Moreover, we were able to prioritize and obtain 10 biological DM risk genes for based on GWAS and PheWAS database analyses, using strict functional annotation criteria, and through gene network expansion to obtain candidate DM drug targets.

In particular, we used seven defined biological criteria to prioritize functional genomic variants, and to identify the biological DM risk genes. In this study, we found 43 overlapping drugs were identified with 13 target genes (*JAK2*, *FCGR3B*, *CD4*, *CD3D*, *LCK*, *CD2*, *CD3E*, *FCGR3A*, *CD3G*, *CD247*, *JAK1*, and *IFNAR2*). Based on clinical and preclinical studies, we showed

that 11 of these new drug candidates were identified as promising drugs for treating DM.

Notably, we showcased the DM target genes, namely *JAK1*, *JAK2*, *IFNAR1*, *IFNAR2 CD4*, and *FCGR3B*, corresponding to nine drug-target combinations that could potentially be repositioned for DM. Remarkably, the identified genes are promising targets for the treatment of DM, as they achieved the highest systemic scores on functional annotations from this study. Importantly, we also found several drug candidates currently under either clinical and/or pre-clinical investigations, five of these drugs targeting the *JAK1* and *JAK2* genes, which supports the clinical and pre-clinical data for DM (*JAK* inhibitors include ruxolitinib, tofacitinib, upadacitinib, baricitinib, and filgotinib). Previous finding has suggested that *JAK1* and *JAK2* are related to DM susceptibility [26].

CD4 T lymphocytes plays an important role in the pathogenesis of DM by triggering antibodies that repair damaged vascular components [27]. We found that drugs that overlap with CD4 include human interferon beta, interferon alpha-2a, and interferon beta-1a. Meanwhile, IFNAR1 and *IFNAR2* are IFN- $\alpha$  receptor subunits that affect DM. As *IFNAR* activates IFN-1, it causes muscle and endothelial cell damage, resulting in DM disease [28]. In addition, interferon beta is a drug that overlaps with IFNAR1 while interferon alpha-1 is a drug that overlaps with INFAR2. Thus, we also identified drugs overlapping with FCGR3B as Human Immunoglobulin G. According to the mechanism of drug action, this can block the Fc receptors by binding to the inhibitory receptors (FcgR2b) of Fc by activating FcgR1 and FcgR3 receptors, thereby suppressing the antibodies [29]. Of note, the expression of identified target genes that are immune-related systemic genes could be specifically transcribed during inflammation or are specific for different skin cells, and could provide further insights into their potential roles in dermatomyositis [30, 31].

It is important to consider both the limitations and the advantages of our approach for drug repositioning for DM. For example, we obtained markedly less genomic variants that encoded our genes of interest. Furthermore, not all the biological risk genes are druggable, this reducing the number of candidate drugs. We believe that the benefits of this approach outweigh the limitations outlined above, because this approach enables the identification of the biological risk genes that could be extended to many other multi-factorial genetic disorders beyond DM. These bioinformatic approaches link the data to the drug database, further narrowing down the candidate drugs for many polygenic diseases, leading to cost and time savings in the drug discovery process.

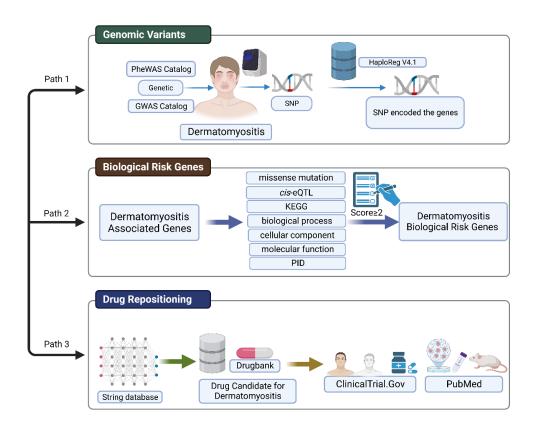
#### 4. Materials and Methods

# 4.1 Workflow for integrative analysis of genomic variants and gene network

A detailed workflow of this study is shown in **Figure 3**. In this study, we prioritize data on DM-associated SNPs. These variants were obtained from the genomic database, namely GWAS and PheWAS catalog databases. In GWAS database, the criteria used for SNPs associated with DM were prioritized based on *p*-value (<10-8) and odds ratio (OR)>1. In PheWAS database, the criteria used for SNPs associated with DM were determined based on *p*-value <0.01 and OR>1. HaploReg database version 4.1 was used to explore the genomic variants. We expanded the range of adjacent SNPs according to the criterion of r<sup>2</sup>> 0.8, this was to obtain more SNPs and genes associated with DM. We realized that the more SNPs that we identified the more candidate genes were found.

To prioritize the risk gene candidates for DM, we use a scoring system with seven functional annotation criteria. Following the scoring system, a total score equal and greater than two (score  $\geq 2$ ) is identified as a DM biological risk gene. In this study, the scoring system was modified based on Okada et al., [32] and applied by Irham et al. for several diseases [33-38]. Next, we used the STRING database to obtain additional DM-targetable genes and the expanded biological DM risk gene. Furthermore, we mapped the biological DM risk genes according to the DrugBank database to identify potential drug targets. ClinicalTrials.gov and PubMed were used to validate the drugs undergoing clinical trials and pre-clinical studies (*in vitro* and *in vivo*, respectively).





**Figure 3.** Schematic model illustrating how the genomic variants can be leveraged for drug repositioning in DM. This figure was created with BioRender.com under agreement number "*FQ24UFDG8T*".

### 4.2 Candidate risk genes associated with dermatomyositis

The SNPs associated with DM were obtained from GWAS and PheWAS catalogs. We ensured that all SNPs were unique without duplicated SNPs. SNPs that fulfill the criterion were utilized for further analysis. In this study, we used HaploReg version 4.1 with r<sup>2</sup>>0.8 criteria to obtain SNPs encoding for DM-related genes. The SNPs encoded genes were prioritized as the genes associated with DM. HaploReg version 4.1 was used to determine the encoded variant genes and further showed the functional role in the pathogenesis of disease through the affected protein [39].

### 4.3 Biological risk genes for dermatomyositis

This study used seven strict functional annotation criteria with a scoring system to prioritize biological DM risk genes. Based on the criteria, each functional annotation is assigned a score of one. A total score of two or more (score  $\geq 2$ ) is required to be classified as a biological risk gene. HaploReg version 4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.p hp) was used to determine the criterion for missense mutation, we considered seven functional annotation criteria, namely: (1) We required missense mutation that was used for functional annotations due to amino acid changes that led to protein function change; (2) *cis*-eQTL was used to determine whether the genetic variants affected protein expression resulting in gene expression changes towards the involved tissue; (3) KEGG was used to determine the involvement of molecular pathways based on KEGG data with a significance false discovery rate (FDR) q <0.05); (4) The biological process was used to determine the genes involved in the biological protein networks and to determine the prioritized inhibitory protein in the biological processes, we considered FDR q < 0.05 as significant; (5) Cellular components; (6) Molecular functions, and (7) PID gene. PID is an innate immune disease that is shown to be associated with DM pathogenesis. The correlation coefficient analysis was performed to determine whether seven functional annotations have possible linear relationships.

#### 4.4 Gene network expansion by using STRING database

The STRING database was used to integrate publicly accessed sources of information by, direct (physical) and indirect (functional) protein-protein interactions. To obtain more potential drug targets, STRING database (<u>https://string-db.org/</u>) was utilized to expand the biological DM risk genes.

#### 4.5 Gene and drug overlapping analysis from drug databases

To obtain new drug targets for DM, overlapping analyses between gene target candidates and drug candidates were conducted using DrugBank (https://go.drugbank.com/) and the drug-gene interaction database (DGIdb) (https://www.dgidb.org/). The requirements for drug targets were candidate drug targets must demonstrate pharmacological activity, guaranteed effectiveness, approved annotations, and clinical trials. We used ClinicalTrial.gov (https://clinicaltrials.gov/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) to verify whether each identified new drug, is under clinical trials for DM or other diseases.

#### 5. Conclusions

The integration of genomic variants and gene network analysis revealed candidate drug targets for dermatomyositis analyzed 1,239 variants (DM). We associated with dermatomyositis and obtained 43 drugs that overlapped with 13 target genes (JAK2, FCGR3B, CD4, CD3D, LCK, CD2, CD3E, FCGR3A, CD3G, IFNAR1, CD247, JAK1, IFNAR2). Interestingly, six drugs overlapped with six target genes were clinically investigated for DM and are candidate drugs that could be repositioned for DM. In addition, we found eight drugs currently under pre-clinical trial that overlapped with the six target genes from our analysis. Overall, this study unveiled novel biological

insights to drive drug discovery for DM by integrating genomic variants and gene network analysis.

### **Author Contributions**

"Conceptualization, L.M.I., Z.A.Z and A.W.S.; methodology L.M.I. Z.A.Z and A.W.S.; software, L.M.I.,W.A.; validation, L.M.I., A.S.L.,Z.A.Z and A.W.S.; formal analysis, L.M.I., M.A., R.C.; investigation, L.M.I., Z.A.Z and A.W.S.; resources, L.M.I., Z.A.Z and A.W.S.; data curation, L.M.I.,W.A. Z.A.Z and A.W.S.; writing—original draft preparation, L.M.I., writing—review and editing, L.M.I., Z.A.Z.,A.W.S.,A.S.L.,M.A. R.C.; visualization, L.M.I.,W.A.S.L.; supervision, Z.A.Z and A.W.S.; funding acquisition, Z.A.Z and A.W.S. All authors have read and agreed to the published version of the manuscript

#### **Declaration of Competing Interest**

The authors disclose no conflict of interest.

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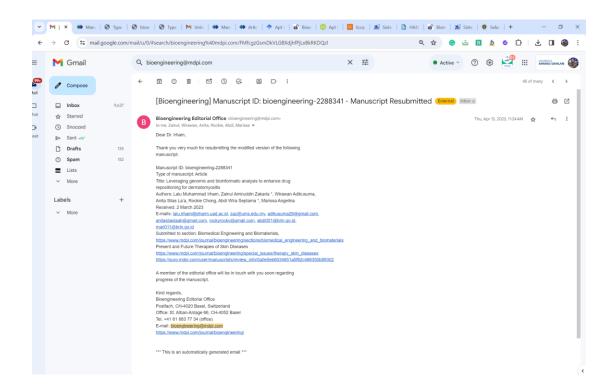
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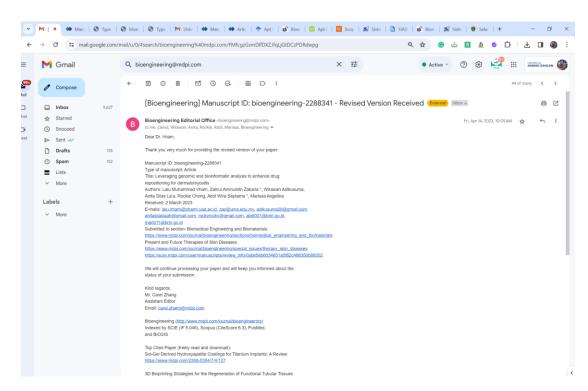
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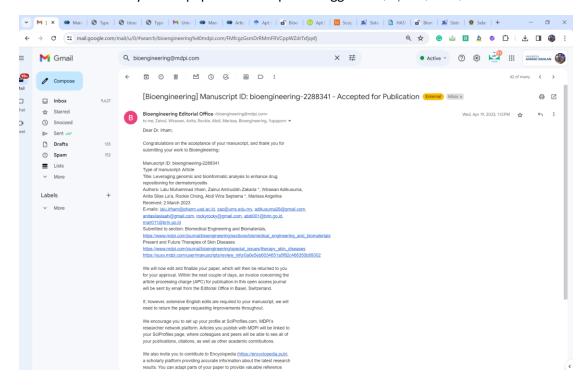


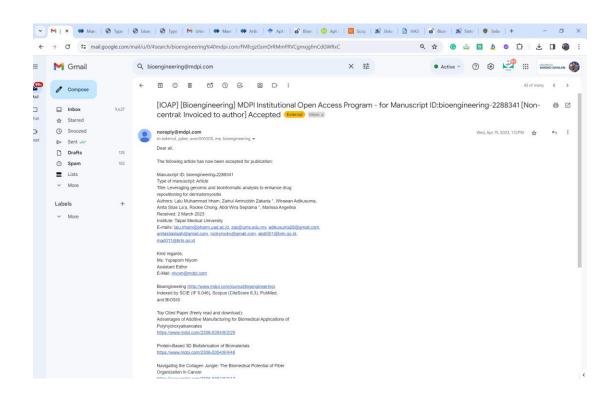
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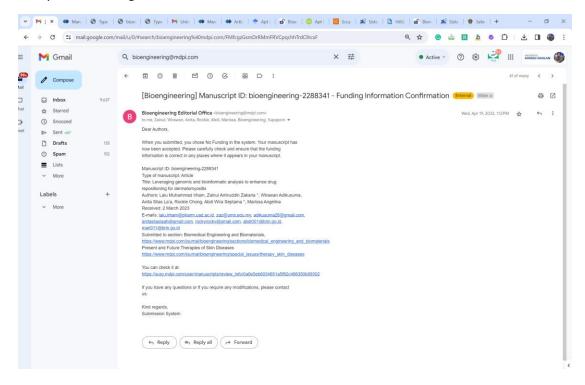


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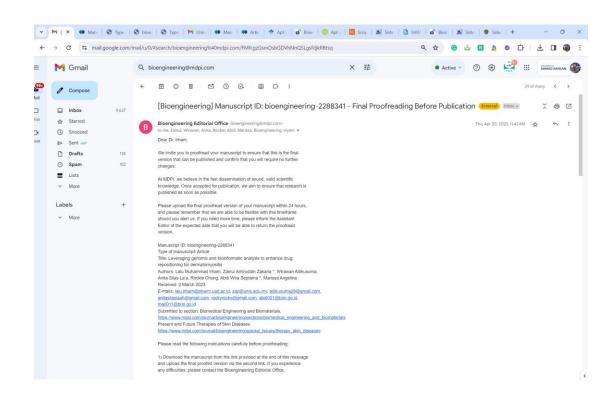




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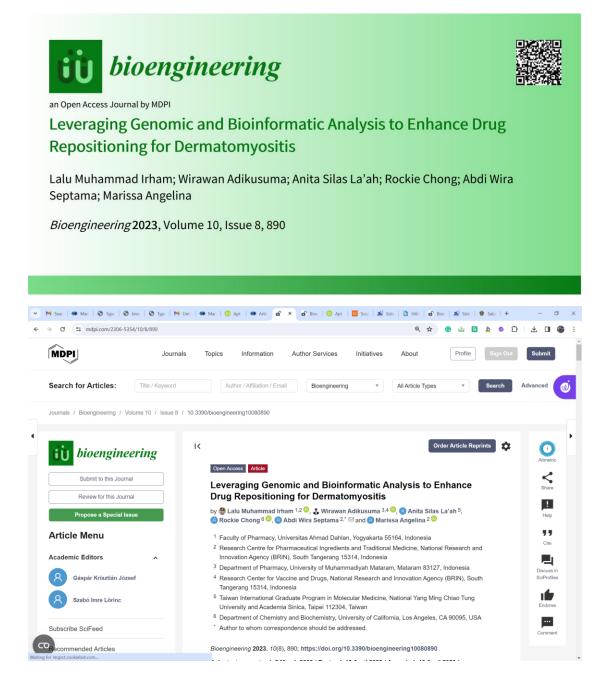
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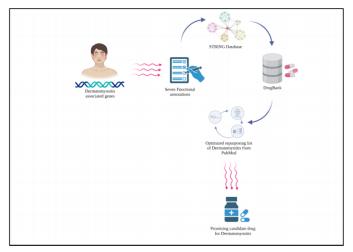
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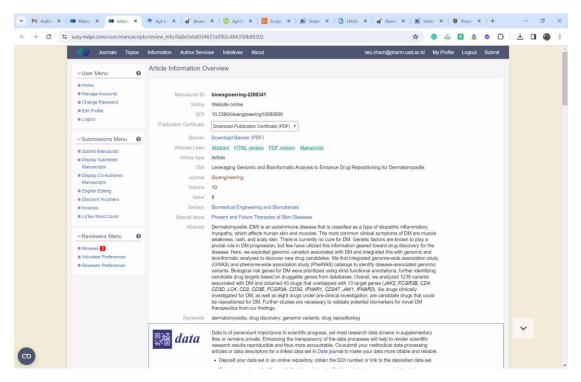
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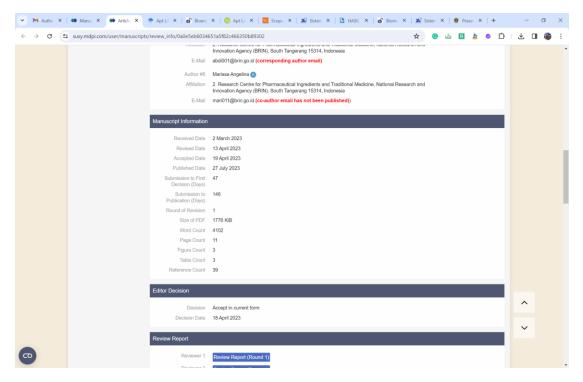
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Leveraging Genomic and Bioinformatic Analysis to Enhance Drug Repositioning for Dermatomyositis

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Abstract: Dermatomyositis (DM) is an autoimmune disease that is classified as a type of idiopathic inflammatory myopathy, which affects human skin and muscles. The most common clinical symptoms of DM are muscle weakness, rash, and scaly skin. There is currently no cure for DM. Genetic factors are known to play a pivotal role in DM progression, but few have utilized this information geared toward drug discovery for the disease. Here, we exploited genomic variation associated with DM and integrated this with genomic and bioinformatic analyses to discover new drug candidates. We first integrated genome-wide association study (GWAS) and phenome-wide association study (PheWAS) catalogs to identify disease-associated genomic variants. Biological risk genes for DM were prioritized using strict functional annotations, further identifying candidate drug targets based on druggable genes from databases. Overall, we analyzed 1239 variants associated with DM and obtained 43 drugs that overlapped with 13 target genes (JAK2, FCGR3B, CD4, CD3D, LCK, CD2, CD3E, FCGR3A, CD3G, IFNAR1, CD247, JAK1, IFNAR2). Six drugs clinically investigated for DM, as well as eight drugs under pre-clinical investigation, are candidate drugs that could be repositioned for DM. Further studies are necessary to validate potential biomarkers for novel DM therapeutics from our findings.

Keywords: dermatomyositis; drug discovery; genomic variants; drug repositioning

#### 1. Introduction

Dermatomyositis (DM) is a rare disease that leads to chronic skin and muscle inflammation, classified as a type of Idiopathic Inflammatory Myopathy [1]. DM is highly prevalent in Asian populations [2,3] and most common in women compared to men between the ages of 40 and 50 years [4]. The etiology of DM involves genetics, immunologic, and environmental factors [1]. For instance, DM has been genetically linked to patients with certain human leukocyte antigen (HLA) types [1]. Some haplotypes associated with high risk include *HLA-A\*68* in North American Whites [5], *HLA-DRB1\*0301* in African Americans [6], and *HLA-DQA1\*0104* and *HLA-DRB1\*07* in Han Chinese [7].

Several symptoms of DM include muscle weakness, myalgia, periungual telangiectasias, dystrophic cuticles, and a reddish rash on the heliotrope around the eyes [8]. In particular, a severe symptom of DM is dystrophic calcinosis, which is the deposition of calcium in the soft tissue of DM patients. This is a very painful condition that commonly affects children and adolescents but is rare in adults [9]. Calcinosis develops within

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