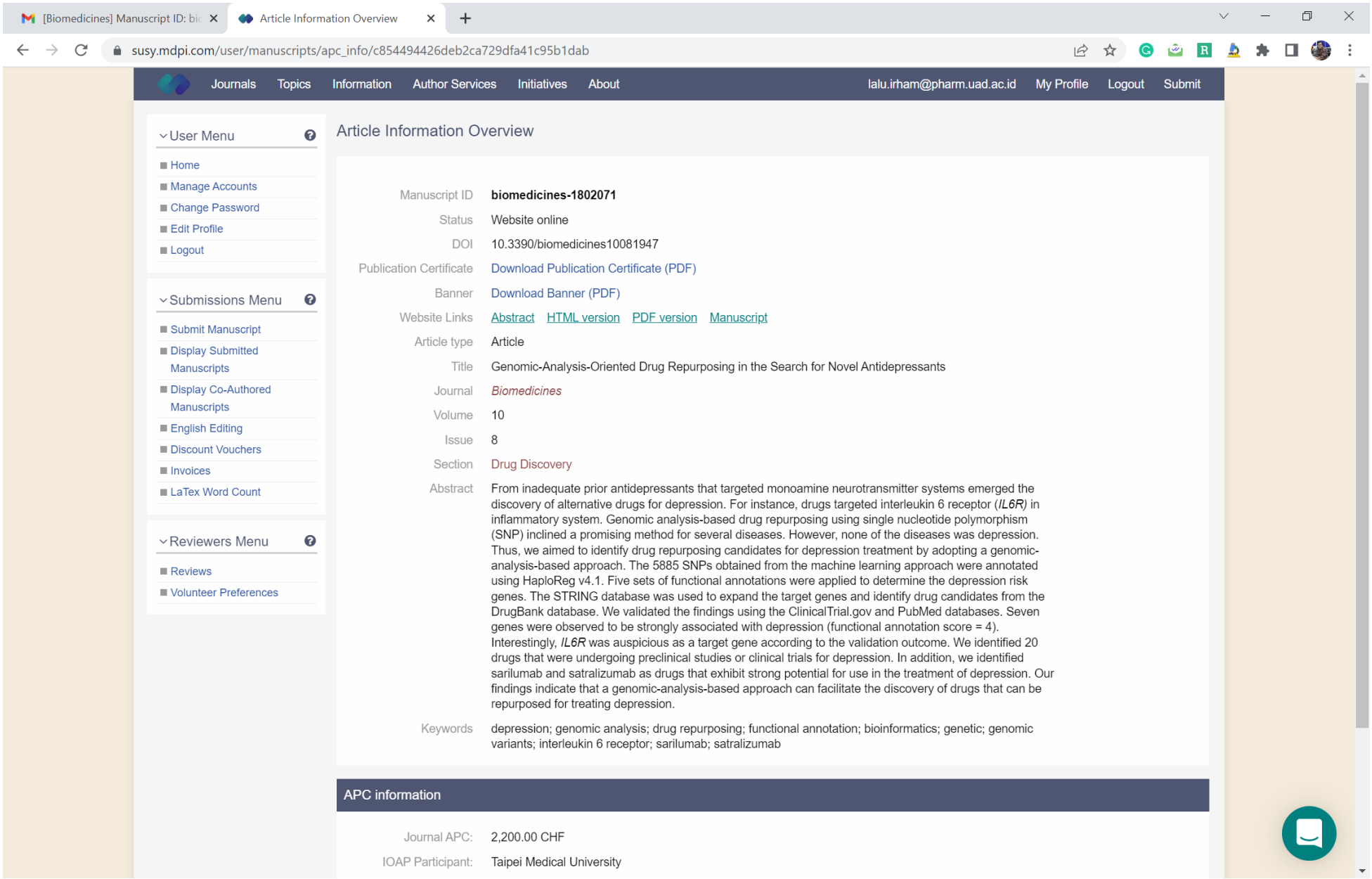
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Title Genomic-Analysis-Oriented Drug Repurposing in the Search for Novel Antidepressants
Journal Biomedicines
Volume 10
Issue 8
Section Drug Discovery
Abstract From inadequate prior antidepressants that targeted monoamine neurotransmitter systems emerged the discovery of alternative drugs for depression. For instance, drugs targeted interleukin 6 receptor (IL6R) in inflammatory system. Genomic analysis-based drug repurposing using single nucleotide polymorphism (SNP) inclined a promising method for several diseases. However, none of the diseases was depression. Thus, we aimed to identify drug repurposing candidates for depression treatment by adopting a genomic-analysis-based approach. The 5885 SNPs obtained from the machine learning approach were annotated using HaploReg v4.1. Five sets of functional annotations were applied to determine the depression risk genes. The STRING database was used to expand the target genes and identify drug candidates from the DrugBank database. We validated the findings using the ClinicalTrial.gov and PubMed databases. Seven genes were observed to be strongly associated with depression (functional annotation score = 4). Interestingly, IL6R was auspicious as a target gene according to the validation outcome. We identified 20 drugs that were undergoing preclinical studies or clinical trials for depression. In addition, we identified sarilumab and satralizumab as drugs that exhibit strong potential for use in the treatment of depression. Our findings indicate that a genomic-analysis-based approach can facilitate the discovery of drugs that can be repurposed for treating depression.
Keywords depression; genomic analysis; drug repurposing; functional annotation; bioinformatics; genetic; genomic variants; interleukin 6 receptor; sarilumab; satralizumab
APC information
Journal APC: 2,200.00 CHF
IOAP Participant: Taipei Medical University

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Genomic-Analysis-Oriented Drug Repurposing in the Search for Novel Antidepressants

Mohammad Hendra Setia Lesmana; Nguyen Quoc Khanh Le; Wei-Che Chiu; Kuo-Hsuan Chung; Chih-Yang Wang; Lalu Muhammad Irham; Min-Huey Chung

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Genomic-Analysis-Oriented Drug Repurposing in the Search for Novel Antidepressants

Authored by:

Mohammad Hendra Setia Lesmana; Nguyen Quoc Khanh Le; Wei-Che Chiu; Kuo-Hsuan Chung; Chih-Yang Wang; Lalu Muhammad Irham; Min-Huey Chung

Published in:

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Article

Genomic-Analysis-Oriented Drug Repurposing in the Search for Novel Antidepressants

Mohammad Hendra Setia Lesmana [1], Nguyen Quoc Khanh Le [2,3,4], Wei-Che Chiu [5,6], Kuo-Hsuan Chung [7,8], Chih-Yang Wang [9,10], Lalu Muhammad Irham [11,*] and Min-Huey Chung [1,12,*]

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Citation: Lesmana, M.H.S.; Le, N.Q.K.; Chiu, W.-C.; Chung, K.-H.; Wang, C.-Y.; Irham, L.M.; Chung, M.-H. Genomic-Analysis-Oriented Drug Repurposing in the Search for Novel Antidepressants. *Biomedicines* **2022**, *10*, 1947. https://doi.org/10.3390/biomedicines10081947

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Abstract: From inadequate prior antidepressants that targeted monoamine neurotransmitter systems emerged the discovery of alternative drugs for depression. For instance, drugs targeted interleukin 6 receptor (*IL6R)* in inflammatory system. Genomic analysis-based drug repurposing using single nucleotide polymorphism (SNP) inclined a promising method for several diseases. However, none of the diseases was depression. Thus, we aimed to identify drug repurposing candidates for depression treatment by adopting a genomic-analysis-based approach. The 5885 SNPs obtained from the machine learning approach were annotated using HaploReg v4.1. Five sets of functional annotations were applied to determine the depression risk genes. The STRING database was used to expand the target genes and identify drug candidates from the DrugBank database. We validated the findings using the ClinicalTrial.gov and PubMed databases. Seven genes were observed to be strongly associated with depression (functional annotation score = 4). Interestingly, *IL6R* was auspicious as a target gene according to the validation outcome. We identified 20 drugs that were undergoing preclinical studies or clinical trials for depression. In addition, we identified sarilumab and satralizumab as drugs that exhibit strong potential for use in the treatment of depression. Our findings indicate that a genomic-analysis-based approach can facilitate the discovery of drugs that can be repurposed for treating depression.

Keywords: depression; genomic analysis; drug repurposing; functional annotation; bioinformatics; genetic; genomic variants; interleukin 6 receptor; sarilumab; satralizumab

1. Introduction

Depression is an emerging mental health problem affecting 322 million people around the world. Southeast Asia and the Western Pacific are the regions where depression is most prevalent [1]. Recent studies conducted in Taiwan reported that the prevalence of depression was 3.7–24.1% [2,3]. Some factors are classed as risk factors of depression, including

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[Biomedicines] Manuscript ID: biomedicines-1802071 - Minor Revisions

1 message

Biomedicines Editorial Office <biomedicines@mdpi.com> Wed, Jul 20, 2022 at 9:06 AM
Reply-To: gloria.wang@mdpi.com
To: Min-Huey Chung <minhuey300@tmu.edu.tw>
Cc: "Moh. Hendra Setia Lesmana" <hendralesmana090294@gmail.com>, Nguyen Quoc Khanh Le <khanhlee@tmu.edu.tw>, Wei-Che Chiu <ppk11642@gmail.com>, Kuo-Hsuan Chung <ch2006ung@tmu.edu.tw>, Chih-Yang Wang <chihyang@tmu.edu.tw>, Lalu Muhammad Irham <lalu.irham@pharm.uad.ac.id>, Biomedicines Editorial Office <biomedicines@mdpi.com>

Dear Dr. Chung,

Thank you again for your manuscript submission:

Manuscript ID: biomedicines-1802071
Type of manuscript: Article
Title: Drug Repurposing for Depression Based on Genomic Analysis
Authors: Moh. Hendra Setia Lesmana, Nguyen Quoc Khanh Le, Wei-Che Chiu, Kuo-Hsuan Chung, Chih-Yang Wang, Lalu Muhammad Irham *, Min-Huey Chung *
Received: 20 June 2022
E-mails: hendralesmana090294@gmail.com, khanhlee@tmu.edu.tw, ppk11642@gmail.com, ch2006ung@tmu.edu.tw, chihyang@tmu.edu.tw, lalu.irham@pharm.uad.ac.id, minhuey300@tmu.edu.tw
Submitted to section: Drug Discovery, https://www.mdpi.com/journal/biomedicines/sections/Drug_Discovery

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(V) Please provide a short cover letter detailing your changes for the editors' and referees' approval.

If one of the referees has suggested that your manuscript should undergo extensive English revisions, please address this issue during revision. We propose that you use one of the editing services listed at https://www.mdpi.com/authors/english or have your manuscript checked by a native English-speaking colleague.

Please do not hesitate to contact us if you have any questions regarding the revision of your manuscript or if you need more time. We look forward to hearing from you soon.

Kind regards,
Ms. Gloria Wang
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This year marks the 10th anniversary of Biomedicines. With the aim of continuously improving our services and increasing the journal's visibility, we have released a survey to gather feedback. Access the survey here: https://www.surveymonkey.com/r/WRKDF9B

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[Biomedicines] Manuscript ID: biomedicines-1802071 - Accept with Minor Revisions

1 message

Biomedicines Editorial Office <biomedicines@mdpi.com> Wed, Jul 27, 2022 at 8:42 AM
Reply-To: gloria.wang@mdpi.com
To: Min-Huey Chung <minhuey300@tmu.edu.tw>
Cc: "Moh. Hendra Setia Lesmana" <hendralesmana090294@gmail.com>, Nguyen Quoc Khanh Le <khanhlee@tmu.edu.tw>, Wei-Che Chiu <ppk11642@gmail.com>, Kuo-Hsuan Chung <ch2006ung@tmu.edu.tw>, Chih-Yang Wang <chihyang@tmu.edu.tw>, Lalu Muhammad Irham <lalu.irham@pharm.uad.ac.id>, Biomedicines Editorial Office <biomedicines@mdpi.com>

Dear Dr. Chung,

We are pleased to inform you that the following paper has been accepted for publication on condition of completing minor revisions:

Manuscript ID: biomedicines-1802071
Type of manuscript: Article
Title: Drug Repurposing for Depression Based on Genomic Analysis
Authors: Moh. Hendra Setia Lesmana, Nguyen Quoc Khanh Le, Wei-Che Chiu, Kuo-Hsuan Chung, Chih-Yang Wang, Lalu Muhammad Irham *, Min-Huey Chung *
Received: 20 June 2022
E-mails: hendralesmana090294@gmail.com, khanhlee@tmu.edu.tw, ppk11642@gmail.com, ch2006ung@tmu.edu.tw, chihyang@tmu.edu.tw, lalu.irham@pharm.uad.ac.id, minhuey300@tmu.edu.tw
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Please revise the manuscript according to the reviewers' comments and upload the revised file within 3 days. Use the version of your manuscript found at the above link for your revisions, as the editorial office may have made formatting changes to your original submission. Any revisions should be clearly highlighted, for example using the "Track Changes" function in Microsoft Word, so that they are easily visible to the editors and reviewers. Please provide a short cover letter detailing any changes, for the benefit of the editors and reviewers.

If the reviewers have suggested that your manuscript should undergo extensive English editing, please have the English in the manuscript thoroughly checked and edited for language and form. Alternatively, MDPI provides an English editing service checking grammar, spelling, punctuation and some improvement of style where necessary for an additional charge (extensive re-writing is not included), see details at https://www.mdpi.com/authors/english.

Do not hesitate to contact us if you have any questions regarding the revision of your manuscript or if you need more time. We look forward to hearing from you soon.

Kind regards,
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This year marks the 10th anniversary of Biomedicines. With the aim of continuously improving our services and increasing the journal's visibility, we have released a survey to gather feedback. Access the survey here: https://www.surveymonkey.com/r/WRKDF9B

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Biomedicines Editorial Office <biomedicines@mdpi.com> Mon, Aug 8, 2022 at 2:37 PM
Reply-To: Gloria Wang <gloria.wang@mdpi.com>, Biomedicines Editorial Office <biomedicines@mdpi.com>
To: Min-Huey Chung <minhuey300@tmu.edu.tw>
Cc: "Moh. Hendra Setia Lesmana" <hendralesmana090294@gmail.com>, Nguyen Quoc Khanh Le <khanhlee@tmu.edu.tw>, Wei-Che Chiu <ppk11642@gmail.com>, Kuo-Hsuan Chung <ch2006ung@tmu.edu.tw>, Chih-Yang Wang <chihyang@tmu.edu.tw>, Lalu Muhammad Irham <lalu.irham@pharm.uad.ac.id>, Biomedicines Editorial Office <biomedicines@mdpi.com>, Gloria Wang <gloria.wang@mdpi.com>

Dear Dr. Chung,

Congratulations on the acceptance of your manuscript, and thank you for submitting your work to Biomedicines:

Manuscript ID: biomedicines-1802071
Type of manuscript: Article
Title: Drug Repurposing for Depression Based on Genomic Analysis
Authors: Moh. Hendra Setia Lesmana, Nguyen Quoc Khanh Le, Wei-Che Chiu, Kuo-Hsuan Chung, Chih-Yang Wang, Lalu Muhammad Irham *, Min-Huey Chung *
Received: 20 June 2022
E-mails: hendralesmana090294@gmail.com, khanhlee@tmu.edu.tw, ppk11642@gmail.com, ch2006ung@tmu.edu.tw, chihyang@tmu.edu.tw, lalu.irham@pharm.uad.ac.id, minhuey300@tmu.edu.tw
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Kind regards,
Shaker A. Mousa
Editor-in-Chief

July 21, 2022

Dear Editors,

Please find our attached manuscript entitled "**Drug Repurposing for Depression Based on Genomic Analysis"** which we are submitting for consideration for publication as an Original Research article in ***Biomedicine*** **(biomedicine-1802071)**. We are thankful for your kind suggestions regarding our manuscript. Here, we are sending our revised manuscript in accordance with the comments given by the two reviewers. We have read through all the reviewers' suggestions very carefully, and made the necessary revisions based on these comments, as detailed below in a point-by-point format. The revised sections are highlighted in yellow. Finally, we would like to thank you once again for giving us the opportunity to improve our manuscript. We very much hope that these revisions are adequate. We appreciate your assistance and are looking forward to hearing from you.

Sincerely yours,

Min-Huey Chung

Professor, College of Nursing,
Taipei Medical University, Taiwan
250 Wu-Hsing Street, Taipei 110, Taiwan

Reviewer 1.

Comments and Suggestions for Authors

The manuscript biomedicines-1802071 entitled Drug Repurposing for Depression Based on Genomic Analysis by Moh. Hendra Setia Lesmana and co-workers, presented a study to identify drug-repurposing candidates for the treatment of depression by adopting a genomic analysis–based approach. Their findings indicate that a genomic analysis–based approach can facilitate the discovery of drugs that can be repurposed for treating depression.

Q1: Reviewer #1. The scientific work was well conducted: the experimental work is consistent with hypothesis and the methodology adequate.
A1: We thank the reviewer's comments

Q2: Reviewer #1. The discussion is consistent with results.
A2: We sincerely thank the reviewer's comment.

Q3: Reviewer #1. Very interesting the importance of IL6, PCR and IL5 with depression: it was already well described a connection between inflammation and depression.
A3: We really appreciate the reviewer's comment.

Q4: **Reviewer #1.** Also, they authors described in addition to IL6 other target genes as CHRNA2, ADORA1 and GABBR1.
A4: We really appreciate the reviewer's comment.

Q5: **Reviewer #1.** The tables and figures should be better formatted for the manuscript. Some tables are divided in two pages (see table 2 and 3 for example).

A5: We thank to the reviewer's suggestion. We replace the figure 1 to be better formatted according to the reviewer's concern.

Q6: There is a section 0 at line 45 which should be removed.

A6: We are very grateful to the reviewer's suggestion**.** We removed already section 0 from line 45-51. Thank you

Reviewer 2.

In the present study Dr. Lesmana and colleagues evaluated drug-repurposing candidates for the treatment of depression adopting a genomic analysis–based approach.
The manuscript is interesting; however, the authors may need to clarify a couple of points.

Comments:

Q1: Reviewer #1. The association between depression and interleukin-6 signaling may need to be further discussed. In this regard, the current literature may need to be updated (e.g Brain Behav Immun. 2021 Jul;95:106-114. doi: 10.1016/j.bbi.2021.02.019).

A1: We are very grateful to the reviewer's suggestions. We did it as suggested by the reviewer. We already adjusted the additional explanation sentences located in the last of discussion part as suggested by the reviewer. The additional of sentences are presented in the following paragraph [**Page 6, lines 251-254**]

Q2: Reviewer #2. The authors found an interesting association between STAT6 gene and depression. However, this topic was not discussed. The authors may need to discuss the importance of STAT6 in depression in both pre-clinical and clinical studies. Is STAT6 a suitable pharmacological target? Moreover, STAT6 has also been correlated with inflammation and cytokine production. Please, discuss this critical point.

A2: Many thanks to the reviewer's suggestions. Yes, it is a very important point. *STAT6* was identified as one of the highest scores based on five-functional annotations in present study. Several studies supported the role of *STAT6* directly with depression which were validated in preclinical investigation, *STAT6* signalling was described to involve in some brain's mechanisms, such as activity of neuron and neuroplasticity[50, 51]. Previous study in animal model emphasized that deficiency of *STAT6* decreased level of dopamine and serotonin transporter, thus, *STAT6* suggested play pivotal role in pathogenesis of depression through monoamines regulation in hippocampus of brain[50, 52]. To date, this result has not been confirmed in clinical study. Unfortunately, the drug target gene that we identified are not all in pharmacological activities including *STAT6*, therefore these might potentially miss the target of the drugs (undruggable)**.** However, we proposed that *STAT6* can be considered as biomarker for depression. We already add the explanation of *STAT6* gene and depression according to the reviewer's suggestions. **[Page 8-9, lines 304-315]**

July 29, 2022

Dear Editors,

Please find our attached manuscript entitled "**Drug Repurposing for Depression Based on Genomic Analysis"** which we are submitting for consideration for publication as an Original Research article in ***Biomedicine*** **(biomedicine-1802071)**. We are thankful for your kind suggestions regarding our manuscript. Here, we are sending our revised manuscript in accordance with the comments given by the academic editor. We have made the necessary revisions based on editor comments by presenting more evidence in the manuscript. The revised sections are highlighted in yellow. Finally, we would like to thank you once again for giving us the opportunity to improve our manuscript. We very much hope that these revisions are adequate. We appreciate your assistance and are looking forward to hearing from you.

Sincerely yours,

Min-Huey Chung

Professor, College of Nursing,
Taipei Medical University, Taiwan
250 Wu-Hsing Street, Taipei 110, Taiwan

Comments and Suggestions for Authors

The manuscript contains three figures, three tables and 52 references. The manuscript was reviewed by two reviewers: Reviewer 1: Minor; and Reviewer 2: Minor. The authors addressed their response properly and the manuscript was revised accordingly. However, the participation of two reviewers was not vigorous enough to improve the quality of the manuscript to meet the standard of the Journal. In my opinion, the number of references is too low for a research article, and this issue may prevent the possibility of publishing it in this form

My overall judgment is to publish this article after the authors have carefully considered my comments by clearing the issues raised and thus by presenting more evidence in the manuscript. I proposed several suggestions that I believe improve the quality of this manuscript. The authors may present their response in a point-to-point manner. I believe that the manuscript carries important value presenting a genomic data analysis-based drug repurposing search for depression. I hope that, after careful revision, the manuscript will meet the high standard of the Journal.

I declare no conflict of interest regarding this manuscript.

It was a great pleasure to participate in the decision session and I am looking forward to hearing from you.

Best regards,

Dr. Masaru Tanaka

Response to reviewer's comment

A2: We sincerely thank the reviewer's comment. We have made the necessary revisions based on editor comments by presenting more evidence in the manuscript. The revised sections are highlighted in yellow. We added the information regarding the *IL6R* regulates systemic inflammation and its association with depression**.** The sentences are as following: ***IL6R* regulates systemic inflammation, which is associated with depression development [27-29] [lines 242-243]**. We also added the information regarding……

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Article

Drug Repurposing for Depression Based on Genomic Analysis

Moh. Hendra Setia Lesmana [1], Nguyen Quoc Khanh Le [2,3,4] Wei-Che, Chiu [5,6] Kuo-Hsuan Chung [7,8] Chih-Yang Wang [9,10] Lalu Muhammad Irham [11,*] and Min-Huey Chung [1,12, *]

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[11] Faculty of Pharmacy, University of Ahmad Dahlan, Yogyakarta, Indonesia 11; lalu.irham@pharm.uad.ac.id
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* Min-Huey Chung, RN, Ph.D.: minhuey300@tmu.edu.tw; Tel.: 886-2-27361661-6317
* Lalu Muhammad Irham, Ph.D.: lalu.irham@pharm.uad.ac.id; Tel: 02-2736-1661

Abstract: Few drugs have been repurposed for the treatment of depression, however, no study has adopted a genomic analysis–based approach in discovering drug-repurposing candidates for depression. This study identified drug-repurposing candidates for the treatment of depression by adopting a genomic analysis–based approach. Using a machine learning algorithm, we identified a total of 5885 genetic variants which were annotated using HaploReg v4.1. Five sets of functional annotations were applied to determine the depression risk genes. The STRING database was used to expand the target genes and identify drug candidates from DrugBank database. We validated the findings using the ClinicalTrial.gov and PubMed databases. Seven genes that were most strongly associated with depression risk (functional annotation score = 4). Interestingly, *IL6R* was identified as the most promising target gene according to the validation. We identified approximately 20 drugs that were undergoing preclinical studies or clinical trials for depression. In addition, we identified sarilumab and satralizumab as drugs that exhibited strong potential for use in the treatment of depression. Our findings indicate that a genomic analysis–based approach can facilitate the discovery of drugs that can be repurposed for treating depression.

Keywords: depression; genomic analysis; drug repurposing

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Academic Editor: Firstname Lastname

Received: date
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1. Introduction

Depression is an emerging mental health problem and it affects 322 million people around the world. Southeast Asia and the Western Pacific are the regions where depression is most prevalent [1]. A study conducted in Taiwan in 2020 reported that the nationwide prevalence of depression was 12.3% [2]. Most currently available antidepressants

were developed on the basis of monoamine neurotransmitter systems and target neural synapses [3]. Three of every ten patients with depression treated with antidepressants have reported treatment resistance [4]. First-line antidepressants often induce insufficient responses. Therefore, discovering alternative targets and potential medications for treating depression is urgent.

Drug repurposing is a common method for identifying potential new treatments using existing drugs [5]. The term "drug repurposing" refers to the repositioning of an existing medicine for a new indication [6]. For example, ketamine was originally approved by the United States Food and Drug Administration (USFDA) in 1970 for use as an intravenous anesthesia agent, but in 2019, it was approved for a new indication: treatment-resistant depression [7,8]. Drug repurposing has some advantages over the conventional method of drug discovery; for example, because drug-repurposing candidates have already passed clinical trials for the original indication, drug repurposing is faster and cheaper than the conventional method [7]. Furthermore, the mechanisms by which repurposed drugs affect the human body are usually already well established [5,9]. Therefore, the safety issue of repurposed drugs has been passed for the use of new indication.

Recent technological developments have encouraged researchers to consider common genetic variants, such as single-nucleotide polymorphisms (SNPs), in drug repurposing [10]. A popular method established by Okada, *et al.* [11] involves utilizing a scoring system comprising eight functional annotations based on genomic analysis to prioritize target genes and discover the drug-repurposing candidates; the method was originally used to identify candidates for the treatment of rheumatoid arthritis according to SNP data collected from genome-wide association studies. Other studies have adapted Okada's approach to use five sets of functional annotations to discover drug-repurposing candidates for the treatment of atopic dermatitis [12] and asthma [13]. Functional annotations are considered crucial for evaluating diseases. Missense variants are nonsynonymous single-base changes that can cause changes in proteins [14]. Cis expression quantitative trait loci (*cis*-eQTL) is observing the variant expressed genes in various tissues [15]. Kyoto Encyclopedia of Genes and Genomes (KEGG) annotations is observing the genetic association that has an important role in the molecular pathway [15]. Molecular pathway analysis related with protein-protein interactions (PPIs) is observing gene contribution in molecular function of an organism [16]. Knockout Mouse Phenotype (KOmice) annotations exhibit considerable overlap with Mammalian Phenotype (MP) Ontology annotations [17]. Accordingly, we postulated that the genomic analysis–based approach using functional annotations could facilitate the discovery of candidates for drug repurposing for the treatment of depression.

Few studies have used SNP data to discover new drugs and drug-repurposing candidates for the treatment of depression. Previous study involving the development of new drugs for treating major depressive disorder (MDD) has focused only on genetic drug-target networks [18]. However, no study has adopted the genomic analysis–based approach using functional annotations to identify drug-repurposing candidates for the treatment of depression. In the present study, we prioritized potential target genes and drug-repurposing candidates for depression by integrating SNP data from the Taiwan Biobank database with a machine learning algorithm by adopting a genomic analysis–based approach and five sets of functional annotations (missense variant, *cis*-eQTL, KEGG, PPI, and KOmice).

2. Materials and Methods

2.1. Study Design

A descriptive schematic of the present study is presented in Figure 1**.** The SNPs were queried from the Taiwan Biobank dataset by using an Extreme Gradient Boost (XGBoost) machine learning algorithm. SNPs connected to other SNPs in the network were retained.

Next, we performed functional annotation of the SNPs according to the five aforementioned sets of functional annotations (missense, *cis*-eQTL, KEGG, PPI, and KOmice) by using HaploReg V4.1. The prioritization of depression-associated genes was based on the scoring system comprising the five sets of functional annotations. The genes that were prioritized and identified as depression risk genes were converted and extended using the STRING database. Thereafter, overlapping of gene targets and drugs was identified using the DrugBank database. Finally, validation was performed using ClinicalTrials.gov and PubMed for drugs that were undergoing clinical trials and preclinical (*in vitro* and *in vivo*) studies, respectively.

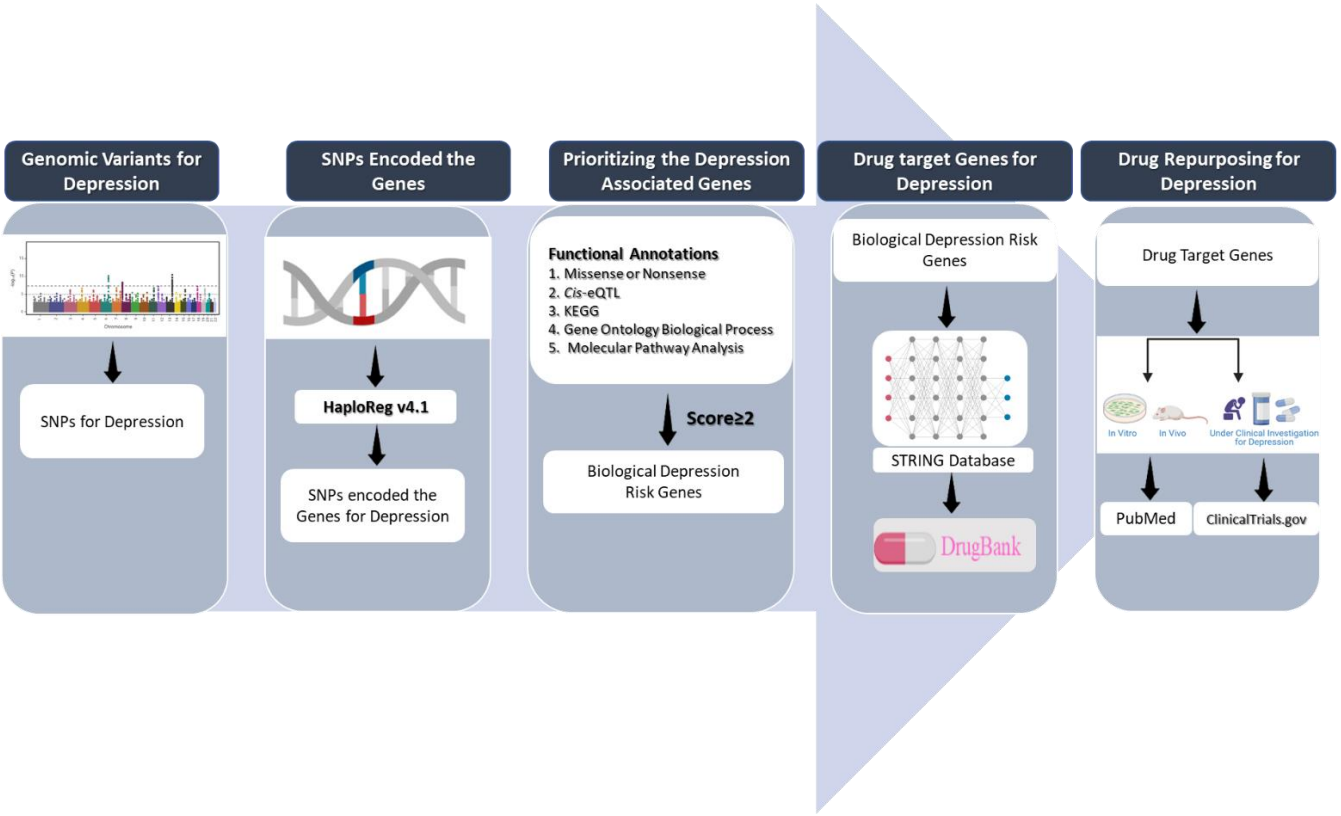

Figure 1. Overview of drug repurposing for depression. In this study design, SNPs were prioritized using a machine learning algorithm and various databases: HaploReg v4.1, STRING, DrugBank, ClinicalTrials.gov, and PubMed.

2.2. Genes Associated with Depression

The SNPs identified using the machine learning algorithm were input into HaploReg v4.1 for functional annotation [19]. HaploReg v4.1 provides thorough information regarding genomic variants and changes in proteins by integrating various functional annotations [19]. Accordingly, the SNPs encoded the genes for depression were obtained and the list of the genes were used in subsequent analyses.

2.3. Five Sets of Functional Annotations for Prioritizing Genes Associated with Depression

A scoring system indicating the most promising target genes integrating the five sets of functional annotations was constructed. The sets of functional annotations were as follows: (i) Missense, to conduct missense functional annotation, we used RStudio v3.4.3 and the HaploR package [20], which contains annotations of functional consequences from a database of SNPs (dbSNPs). Because changes in the amino acid sequences might alter protein function, missense or nonsense variants can be considered as one of the important functional annotations. The genes with missense SNPs associated with depression were assigned 1 point. (ii) *Cis*-eQTLs, A *cis*-eQTL SNP affects the expression of the gene at the location of the SNP [21]. The SNP is linked to a shift in gene expression in the target tissue, which has physiological consequences. Any gene with a *cis*-eQTL SNP associated with depression expressed in whole blood was given 1 point. (iii) KEGG, The KEGG, an online biochemical route database, was used to perform molecular pathway enrichment analysis [22]. Genes that were abundant in the KEGG pathway (false discovery rate [FDR] of 0.05) were each assigned 1 point [23]. (iv) PPI, the biological process category of Gene Ontology was used as a data source. An FDR of 0.05 was established as the threshold for significance [23]. (v) KO mice, to query the mouse phenotype, BioMart was used to convert the human gene Ensemble IDs were converted to mouse gene Ensemble IDs [24]. The Mammalian Phenotype Ontology Browser, which includes information on mice and other mammalian phenotypes, was used as a data source. The gene set was considered significant when the FDR in the enrichment analysis was <0.05.

According to our functional annotation, genes with one functional annotation were assigned 1 point, and genes with a score of ≥2 points were identified as biological depression risk genes.

2.4. STRING and Drugbank Analysis

The STRING database provides information related to gene-encoded proteins. The identified depression risk genes were subjected to STRING analysis according to the proteins that they encoded [25]. The proteins encoded by the identified genes were considered potential drug targets and were subjected to further analysis conducted using DrugBank, a large database (www.drugbank.ca) with data on over 17,000 drug targets and 10,000 drug compounds [26].

2.5. Validation of Target Genes for Depression

The drugs identified from DrugBank were confirmed through two databases: ClincalTrial.gov (https://clinicaltrials.gov/) was used for the drugs undergoing human trials, and PubMed was used for the drugs undergoing preclinical (*in vitro* and *in vivo*) studies.

3. Results

We identified 5885 SNPs associated with depression (Supplementary Table 1.), 632 of which were unique. The genes with the identified SNPs were identified as depression-associated genes (Supplementary Table 2.).

Depression Risk Genes Identified Using Functional Annotations

We assigned each of the 632 unique depression-associated genes a score according to their functional annotations. The distribution of the functional annotations is illustrated in Figure 2. We used the missense variant and cis-eQTL annotations as the first and second criteria for identifying and prioritizing the depression-associated genes. Overall, 34 and 68 of the depression-associated genes had missense and cis-eQTL SNPs, respectively. The third set of criteria for consideration of a depression-associated gene was the Gene Ontology annotations. We identified 87 genes depression-associated genes. The fourth set of criteria was the PPI annotations. We identified 59 genes that overlapped with the depression-associated genes. The fifth set of criteria, the KEGG annotations, was used to perform enrichment analysis on the molecular pathways. Sixteen depression-associated genes were identified in the KEGG-annotated pathways according to the enrichment analysis.

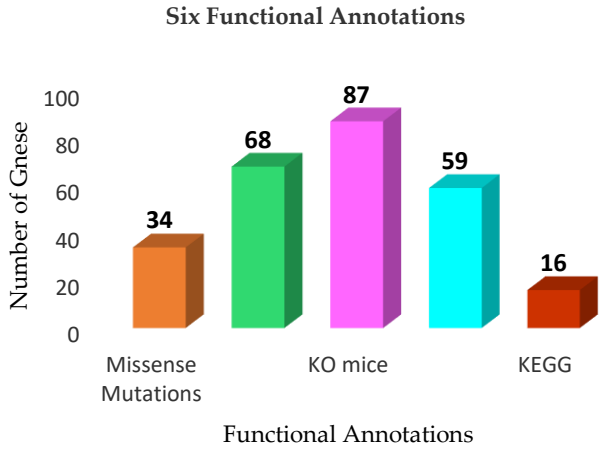

Figure 2. Histogram distribution of functional annotations.

We compiled the scores of each of the genes (from 0 to 4 points) according to their functional annotations **(**Figure 3). The largest proportion of the genes (460 genes) had a score of 0 points. A total of 65 genes had scores ≥2 and were thus identified as depression risk genes (Table 1). Only seven of the genes—*Interleukin 4 (IL4), Interleukin 18 Receptor 1 (IL18R1), Interleukin 6 Receptor (IL6R), Signal Transducer And Activator Of Transcription 6 (STAT6), SMAD Family Member 3 (SMAD3), Interleukin 13 (IL13)*, and *Toll Like Receptor 1 (TLR1)*—had a score of 4 points.

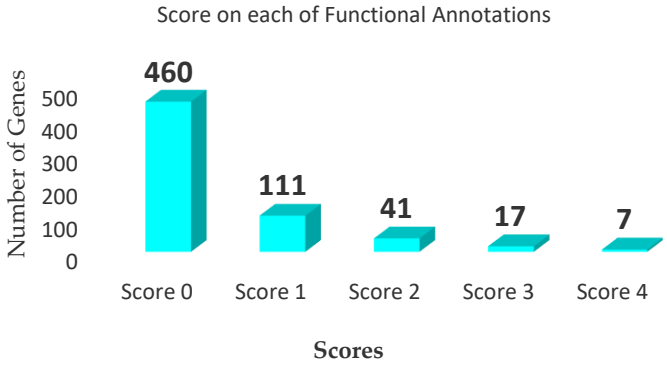

Figure 3. Histogram distribution of gene scores: 460 and 111 genes had scores of 0 and 1, respectively; the 65 genes with total scores ≥2 were identified as "depression risk genes.".

188 **Table 1. Five functional annotations applied to prioritized the** depression risk genes.

GENCODE_id	GENCODE_name	Missense Variant	Cis-eQTL	KEGG	PPI	KOmice	Total Score
ENSG00000113520	*IL4*	0	1	1	1	1	4
ENSG00000115604	*IL18R1*	0	1	1	1	1	4
ENSG00000160712	*IL6R*	1	1	0	1	1	4
ENSG00000166888	*STAT6*	0	1	1	1	1	4
ENS G00000166949	*SMAD3*	0	1	1	1	1	4
ENSG00000169194	*IL13*	1	0	1	1	1	4
ENSG00000174125	*TLR1*	1	1	0	1	1	4
ENSG00000020633	*RUNX3*	0	1	0	1	1	3
ENSG00000069667	*RORA*	0	0	1	1	1	3
ENSG00000107485	*GATA3*	0	0	1	1	1	3
ENSG00000109471	*IL2*	0	0	1	1	1	3
ENSG00000113525	*IL5*	0	0	1	1	1	3
ENSG00000115602	*IL1RL1*	1	0	0	1	1	3
ENSG00000117586	*TNFSF4*	0	1	0	1	1	3
ENSG00000125347	*IRF1*	0	1	0	1	1	3
ENSG00000134215	*VAV3*	0	1	0	1	1	3
ENSG00000138684	*IL21*	0	0	1	1	1	3
ENSG00000141736	*ERBB2*	1	0	0	1	1	3
ENSG00000158869	*FCER1G*	0	1	0	1	1	3
ENSG00000161405	*IKZF3*	0	1	0	1	1	3
ENSG00000179344	*HLA-DQB1*	0	1	1	0	1	3
ENSG00000204252	*HLA-DOA*	0	0	1	1	1	3
ENSG00000204287	*HLA-DRA*	1	1	1	0	0	3
ENSG00000231389	*HLA-DPA1*	0	1	1	1	0	3
ENSG00000073605	*GSDMB*	1	1	0	0	0	2
ENSG00000074047	*GLI2*	0	0	0	1	1	2
ENSG00000079112	*CDH17*	0	0	0	1	1	2
ENSG00000087086	*FTL*	0	0	0	1	0	2
ENSG00000087088	*BAX*	0	0	0	1	1	2
ENSG00000100385	*IL2RB*	0	1	0	0	1	2
ENSG00000100902	*PSMA6*	0	1	0	0	0	2
ENSG00000106571	*GLI3*	0	0	0	1	1	2
ENSG00000107957	*SH3PXD2A*	1	0	0	0	1	2
ENSG00000111145	*ELK3*	1	0	0		1	2
ENSG00000111335	*OAS2*	1	1	0		0	2
ENSG00000112130	*RNF8*	0	0	0	1	1	2
ENSG00000112486	*CCR6*	0	0	0	1	1	2
ENSG00000113522	*RAD50*	0	0	0	0	1	2
ENSG00000120903	*CHRNA2*	0	1	0	0	1	2

Table 1. (Continue). Five functional annotations applied to prioritized the depression risk genes.

ENSG00000124107	*SLPI*	0	0	0	1	1	2
ENSG00000131507	*NDFIP1*	0	0	0	1	1	2
ENSG00000134460	*IL2RA*	0	0	0	1	1	2
ENSG00000134470	*IL15RA*	0	1	0	0	1	2
ENSG00000135905	*DOCK10*	0	0	0	1	1	2
ENSG00000137033	*IL33*	0	0	0	1	1	2
ENSG00000142556	*ZNF614*	1	1	0	0	0	2
ENSG00000143631	*FLG*	1	0	0	0	1	2
ENSG00000145777	*TSLP*	0	0	0	1	1	2
ENSG00000162104	*ADCY9*	0	1	0	0	1	2
ENSG00000163485	*ADORA1*	0	1	0	0	1	2
ENSG00000165280	*VCP*	0	0	0	1	1	2
ENSG00000167914	*GSDMA*	1	1	0	0	0	2
ENSG00000171132	*PRKCE*	0	0	0	1	1	2
ENSG00000171608	*PIK3CD*	0	0	0	1	1	2
ENSG00000172057	*ORMDL3*	0	1	0	1	0	2
ENSG00000174130	*TLR6*	0	0	0	1	1	2
ENSG00000179588	*ZFPM1*	0	0	0	1	1	2
ENSG00000180902	*D2HGDH*	1	1	0	0	0	2
ENSG00000186265	*BTLA*	0	0	0	1	1	2
ENSG00000186716	*BCR*	0	1	0	1	0	2
ENSG00000196735	*HLA-DQA1*	0	1	1	0	0	2
ENSG00000197746	*PSAP*	0	0	0	1	1	2
ENSG00000198821	*CD247*	0	1	0	0	1	2
ENSG00000204681	*GABBR1*	1	0	0	0	1	2
ENSG00000215182	*MUC5AC*	1	0	0	0	1	2

STRING Database for Gene-Set Expansion

The STRING database, which combines publicly available data on direct (physical) and indirect (functional) protein–protein interactions, was used to extend the gene set of the 65 depression risk genes. Fifty interactions were selected from the database, and ultimately, 115 genes were selected as target genes and used in subsequent analyses (Supplementary Table 3).

Prioritization of Drug-Repurposing Candidates for Depression

The DrugBank database was used to identify the druggable genes from among the 115 genes identified in the STRING analysis. Unfortunately, not all of the depression risk genes were druggable; only 19 of the genes were identified as druggable and determined to bind with 58 drugs. Of the seven genes with a score of 4 points, only *IL6R* was determined to be druggable. All the identified target genes and drugs are listed in Supplementary Table 4.

Intriguingly, of the 58 identified drugs, 20 were undergoing clinical trials or preclinical studies for depression (Table 2). The other 38 drugs were new drugs that had never been previously reported to be used for the treatment of depression.

Table 2. Pharmacological Therapies in Development for the Treatment of Depression.

Gene	Drug	Original Indication	Identifier* (NCT-0/PMID)
ClinicalTrials.gov			
FTL	Iron Dextran	Iron deficiency	3373253
IL5	Mepolizumab	Eosinophilic granulomatosis with polyangiitis (EGPA)	4680611
IL6R	Tocilizumab	Rheumatoid arthritis	3787290
ADORA1	Tramadol	Moderate to severe pain	3309163
ADORA1	Caffeine	Migraine	0025792
ADORA1	Theophylline	Chronic asthma	1263106
ADORA1	Adenosine	Tachycardia	2902601
ADORA1	Pentoxifylline	Intermittent claudication	4417049
PRKCE	Tamoxifen	Breast cancer	0667121
CHRNA2	Mecamylamine	Hypertension	0593879
CHRNA2	Rocuronium	General anesthesia	4565730
GABBR1	Taurine	Total parenteral nutrition	0217165
PubMed			
CD3D	Muromonab	Prevention of organ rejection	24257035
CD247	Muromonab	Prevention of organ rejection	24257035
ADORA1	Dyphylline	Asthma	10064181
CHRNA2	Carbamoylcholine	Open angle Glaucoma	23603524
CHRNA2	Cisatracurium	General anesthesia	22092267
CHRNA2	Atracurium besylate	General anesthesia	8442962
CHRNA2	Mivacurium	General anesthesia	8346843
CHRNA2	Vecuronium	Muscle relaxant	8733812

*Identifiers from ClinicalTrials.gov and PubMed database.

The target genes were those reported in preclinical studies and clinical trial studies to be the most promising target genes for depression. We identified nine target genes, including *CD3 Delta Subunit Of T-Cell Receptor Complex* (*CD3D*), *CD247 Molecule (CD247)*, *Adenosine A1 Receptor (ADORA1)*, *Cholinergic Receptor Nicotinic Alpha 2 Subunit (CHRNA2)*, *Protein Kinase C Epsilon (PRKCE)*, *Ferritin Light Chain (FTL)*, *Interleukin 5 (IL5)*, *Gamma-Aminobutyric Acid Type B Receptor Subunit 1 (GABBR1), and IL6R*. Of the 38 new drugs, the following 15 targeted six of the most promising target genes: sodium ferric gluconate complex, ferric pyrophosphate citrate, blinatumomab, reslizumab, sarilumab, satralizumab, aminophylline, oxtriphylline, metocurine iodide, doxacurium, tubocurarine, decamethonium, metocurine, pancuronium, and pipecuronium (Table 3). Of these, we highlight sarilumab and satralizumab as exhibiting the most potential as drug-repurposing candidates for depression because they target *IL6R*, which was identified as the gene exhibiting the strongest potential as a target gene according to the functional annotation scoring system and the validation conducted using the ClinicalTrials.gov and PubMed databases (Table 3).

Table 3. Drug-Repurposing Candidates for Depression Identified Using a Genomic Analysis–Based Approach.

Biological Gene	Target Drug	Original Indication	Score
IL6R	Sarilumab	Rheumatoid arthritis	4
IL6R	Satralizumab	Neuromyelitis optica spectrum disorder (NMOSD)	4
IL5	Reslizumab	Severe asthma	3
sFTL	Sodium ferric gluconate complex	Iron deficiency anemia	2
FTL	Ferric pyrophosphate citrate	Iron deficiency	2
CD3D	Blinatumomab	Acute lymphoblastic leukemia (ALL)	2
ADORA1	Aminophylline	Asthma	2
ADORA1	Oxtriphylline	Asthma	2
CHRNA2	Metocurine iodide	Muscle contractions	2
CHRNA2	Doxacurium	General anesthesia	2
CHRNA2	Tubocurarine	General anesthesia	2
CHRNA2	Decamethonium	Muscle relaxant	2
CHRNA2	Metocurine	Muscle relaxant	2
CHRNA2	Pancuronium	Muscle relaxant	2
CHRNA2	Pipecuronium	Muscle relaxant	2

Note: Scores were obtained from a scoring system based on five sets of functional annotations.

4. Discussion

This study integrated machine learning and functional annotations to identify drug-repurposing candidates for the treatment of depression. We identified seven key depression risk genes according to their highest functional annotation scores and identified *IL6R* as the most promising target gene for depression according to clinical and preclinical evidence. In addition, we identified approximately 20 drugs undergoing clinical trials and preclinical studies for use in the treatment of depression and 15 new drug-repurposing candidates, including sarilumab and satralizumab, exhibiting strong potential for use in the treatment of depression. These findings indicate that adopting a genomic analysis–based approach to drug repurposing can facilitate the discovery of new drugs for treating depression.

IL6R was one of the target genes with the highest functional annotation score and was a highly promising target in the treatment of depression. *IL6R* regulates systemic inflammation, which is associated with depression development [27]. Genetic variants of *IL6R* are associated with interleukin 6 (IL6) and C-Reactive Protein (CRP) regulation [28]. The upregulation and downregulation of IL6 and CRP affect depression severity [27,28]. According to a previous study, the increasing number of soluble interleukin 6 receptor (sIL6R) in the trans signaling significantly induced the odds of depression. In addition, high level of sIL6R associated with lower CRP production through classical signaling, which indicated a high risk of depression[29]. Tocilizumab, which is undergoing clinical studies under accession number NCT03787290, is a humanized monoclonal antibody that targets *IL6R*, thereby inhibiting IL6 classic signaling and trans-signaling [30], and is effective in alleviating depressive symptoms [31]. In addition, we identified two other drugs that target *IL6R*: sarilumab and satralizumab. Although no evidence regarding the use of these two drugs in the treatment of depression has been uncovered, they exhibit strong potential as drug-repurposing candidates for depression.

IL5 encodes a cytokine that is an effector cytokine of activated Th2 cells; that is, IL5 activates Th cells after the cells are activated by IL4 [32]. *IL5* plays key roles in some autoimmune diseases. The elevated IL13 levels and lower IFN-γ levels were associated with depression. In addition, the similarity between the main functions of IL13 and IL5 suggests that depression may also be associated with IL5 levels [33]. This finding was supported by a gene-set analysis study in which *IL5* was upregulated in the post-mortem brain tissue of a patient with MDD [34]. A confirmation study that investigated the association between IL5 and MDD in 116 participants (MDD = 58; control = 58) revealed that every 1-unit increase in serum IL5 level was associated with a 76% greater risk of MDD [21]. Mepolizumab is a fully humanized recombinant IgG1 kappa monoclonal antibody against *IL5* and has been approved for severe asthma. In a previous study, mepolizumab administered for 6 months significantly reduced the occurrence of asthma exacerbations (from 48% to 38%) in patients with asthma and comorbid depression [35]. Mepolizumab is undergoing clinical trials for depression in patients with asthma (accession number: NCT-04680611). Another drug candidate identified in the present study is reslizumab, which targets *IL5*. We assumed that the mechanisms underlying the effect of reslizumab on the pathophysiology of depression involved *IL5*.

Nickell, *et al.* [36] investigated the role of *CHRNA2* in depression by assessing its various functions in the cholinergic nervous system, especially its ability to activate cholinergic signals in the central nervous system by mediating muscarinic and nicotinic receptor activation. CHRNA2 is a widely expressed subunit of nicotinic acetylcholine receptors and is involved in neurocognitive disorders and nicotine dependence. The position of *CHRNA2* in chromosomes (in the 8p region) may be involved in neurodegenerative and psychiatric disorders [37]. In the present study, carbamoylcholine, cisatracurium, atracurium besylate, mivacurium, vecuronium, and two drugs of which the clinical efficacy was confirmed through clinical trials (mecamylamine and ruconium) were determined to target *CHRNA2*. The non-competitive antagonist mecamylamine, a widely used therapeutic agent that targets acetylcholine receptors, may be effective in depression treatment [36]. In addition, reconium, originally used as a muscle relaxant, may have antidepressant effects and is an effective adjunctive treatment with electroconvulsive therapy (ECT) [38,39]. Rocunium has been observed to reduce myalgia and headache and shorten the awakening time (spontaneous respiration and opening the eyes in response to verbal stimuli) after ECT [39].

Another target gene that we identified in the current study was *ADORA1*, which regulates various biological functions, including the mechanisms underlying sleep and psychiatric disorders. *ADORA1* activation has antidepressant effects. In addition, the therapeutic effects of sleep deprivation [40] and ECT [41] are mediated by the activation or upregulation of *ADORA1*. Tramadol, a drug undergoing phase IV clinical trials for depression, was determined to target *ADORA1* in the present study. Bumpus [42] assessed patients' perceptions of the effectiveness and safety of tramadol as an off-label antidepressant relative to 34 other antidepressants and discovered that most (94.6%) of the patients viewed tramadol as an effective antidepressant. Tramadol is a mu-receptor opioid agonist that increases the concentrations of serotonin and noradrenaline in the limbic system, thereby exerting an antidepressant effect [43]. In addition to tramadol, we identified other drugs linked to *ADORA1*, including caffeine, theophylline, adenosine, and pentoxifylline, that were undergoing phase 1 and 2 clinical trials. Furthermore, we discovered other target genes and drug-repurposing candidates for depression of which the efficacy is supported by published evidence, such as muromanab, which targets *CD3D*/*CD247* [44,45], and taurine, which targets *GABBR1* [46,47].

In addition, in term of neuro-inflammation, *STAT6* was found to be associated with neurodegeneration disease including depression [48,49]. Interestingly, *STAT6* was one of the highest scores based on five-functional annotations in the present study. Several studies supported the role of *STAT6* in depression, which were validated in a preclinical investigation, *STAT6* signaling was described to involve in some brain's mechanisms, such

as the activity of neurons and neuroplasticity [50,51]. Previous studies in animal model emphasized that deficiency of STAT6 decreased level of dopamine and serotonin transporter, thus, *STAT6* suggested play pivotal role in pathogenesis of depression through monoamines regulation in hippocampus of brain [50,52]. To date, this result has not been confirmed in clinical study. Unfortunately, the drug target gene that we identified are not all in pharmacological activities (undruggable) including *STAT6*. However, we proposed that *STAT6* can be considered as a potential biomarker for depression.

Despite the fact that our study demonstrates the feasibility and value of using SNP data to determine drug-repurposing candidates for the treatment of depression, it still has some limitations. Not all SNPs are biologically significant, and not all the identified depression risk genes could be targeted by drugs. In addition, the molecular mechanisms underlying the antidepressant effects of the identified drug-repurposing candidates have not been validated and therefore warrant further investigation.

5. Conclusions

In this study, using a genomic analysis–based approach, we discovered drug-repurposing candidates for depression that are undergoing clinical trials and preclinical studies. Moreover, we identified *IL6R* as the most promising target gene for depression because it had the highest functional annotation score as well as it's validation and identified two candidates (sarilumab and satralizumab) with strong potential use in the treatment of depression. In summary, this study indicates that using a genomic analysis–based approach to discovering drugs for treating depression is both time- and cost-effective. Furthermore, the findings of our study can serve as a reference for future studies investigating the role of *IL6R* in the pathogenesis of depression as well as the interactions between *IL6R* and sarilumab or satralizumab.

Supplementary Materials: Table S1: SNP Prioritization; Table S2: Scoring 5 function annotation; Table S3: Protein annotation STRING; Table S4: Druggable Bio genes; Table S5: PubMed Drug Search

Author Contributions: conceptualized: M.H.S.L., and M.H.C. Data curation: N.Q.K.L., K.H.C., W.C.C., and C.Y.W. Data analysis: M.H.S.L., and L.M.I. Data interpretation: M.H.S.L., L.M.I., and M.H.C. Original manuscript writing: M.H.S.L. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy

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