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Article

From Genomics to Therapy: Repurposing Approved Drugs and Identifying Novel Targets for Sickle Cell Disease in Saudi Patients

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Abstract

Background: Sickle cell disease (SCD) is an inherited blood disorder characterized by chronic hemolysis, inflammation, and vaso-occlusive crises (VOC), leading to several complications and reduced life expectancy of affected individuals. Limited effective treatment options are currently available; however, pharmacogenomic (PGx) insights derived from recent genomic findings, particularly in underrepresented populations such as Saudi Arabians, may offer new hope for predicting molecular-guided treatments. This study aimed to identify approved drugs suitable for repurposing based on their interaction with SCD-associated genetic variants and discover novel druggable targets within genetic pathways linked to disease severity by utilizing genome-wide association study (GWAS) data from Saudi SCD patients.

Methods: Our PGx analysis used bioinformatic pipelines to evaluate drug-gene interactions and identify potential therapeutic targets to treat SCD based on GWAS data derived from the Saudi population. Selected approved drugs were suggested for repurposing based on their interactions with genes of interest known to impact SCD pathophysiology, using the Drug-Gene Interaction Database (DGIdb 5.0). New drug targets were also proposed based on assessing the simulated pockets of gene products according to the 3D protein structures provided by the protein data bank (PDB) and the AlphaFold database. New molecules with higher druggability scores, estimated based on the DoGSiteScorer database, were predicted to have a higher success rate in developing new SCD treatments.

Results: Our analysis identified 78 approved medications that showed potential for repurposing in SCD; this list was narrowed down to 21 candidates based on their safety profiles and interactions with key genetic pathways in SCD. Among them, simvastatin, allopurinol, omalizumab, canakinumab, and etanercept were suggested as the most promising agents. Furthermore, novel drug targets encoded by olfactory receptor (OR) gene clusters (OR51V1, OR52A1, OR52A5, OR51B5, and OR51S1), TRIM genes, SIDT2, and CADM3, had high druggability scores.

Conclusion: This study provides a robust framework for drug repurposing and novel drug discovery in SCD, particularly tailored to the Saudi population. The findings underscore the potential of leveraging genomic data to identify targeted therapies, offering a pathway to more personalized and effective treatments for SCD patients. Future clinical trials are essential to validate these findings and translate them into clinical practice.

Keywords: Sick cell disease; Drug repurposing; Saudi population; Precision medicine; Pharmacogenomics

1. Introduction

Sickle cell disease (SCD) is a distressing inherited hematological disorder caused by a pathological hemoglobin variant (*rs334* c.20 A>T) in the *HBB* gene, which induces rigid deformation or “sickling” of red blood cells (erythrocytes)¹. This sickling leads to a range of downstream vascular complications, including vaso-occlusive episodes, thrombosis, and multiorgan infarctions, contributing to the clinical severity of SCD from early childhood onward^{1,2}. The severe nature of these complications is further highlighted by the reduced life expectancy among patients compared to unaffected individuals in the general population³.

From a public health perspective, SCD imposes a substantial global burden, with recent estimates indicating that over 7 million individuals live with the disease worldwide, with the highest prevalence found in sub-Saharan Africa, where the sickle cell trait has been historically promoted by the region's malaria endemicity⁴. Significant burdens also exist in India, the Americas, the Mediterranean, and the Middle East, though accurate epidemiological data is often limited by inadequate surveillance and historically high childhood mortality rates⁵.

Reflecting this global burden, Saudi Arabia faces a notably high prevalence of SCD, with carrier rates nearing 27% and disease prevalence reaching 2.6%^{6,7}. This substantial burden is likely exacerbated by high rates of consanguineous marriages, which concentrate inherited disease variants^{6,8}.

Despite the significant unmet medical need, the range of approved therapies for SCD remains remarkably limited. Initially, hydroxyurea was the only treatment approved by the US FDA for both adults and children with SCD. Since 2017, the therapeutic landscape has evolved, with the US FDA approving three new agents targeting distinct aspects of SCD pathophysiology, including: L-glutamine, crizanlizumab, and voxelotor^{9,10}. However, recent developments have highlighted the challenges in this field. Notably, as of September 2024, voxelotor was voluntarily withdrawn globally due to safety concerns, and in May 2023, crizanlizumab was withdrawn from the European market^{11,12}. These events underscore the complexities of SCD treatment and emphasize the critical importance of ongoing research, rigorous long-term safety monitoring, and continuous re-evaluation of approved therapies.

While bone marrow transplantation (BMT) offers a potential cure, its application is often hindered by significant challenges, including high costs, donor availability, and associated risks. The recent approval of the first cell and gene therapies, Casgevy and Lyfgenia, on December 8, 2023, marked a substantial advancement in SCD treatment. However, these cutting-edge therapies remain inaccessible to many patients due to their extremely high costs¹³. This situation highlights the urgent need for further research into innovative therapies that offer safer, more effective, and affordable treatment options for SCD.

Furthermore, the complex genetic nature of SCD, coupled with recently identified disease-associated genetic variants from genome-wide association studies (GWAS), presents an ideal opportunity for pharmacogenomic (PGx) approaches to guide both drug repurposing efforts and novel therapeutic development.^{14,15} Drug repurposing represents a systematic methodology to propose new indications for currently marketed drugs based on their interactions with key genes that modulate cellular pathways and potentially ameliorate disease outcomes¹⁶. This computationally

driven approach, which relies on in silico gene target analyses, has been used effectively to repurpose multiple drugs for various disease conditions¹⁷.

Our research focuses on repurposing existing drugs and discovering new molecules for SCD, which would then undergo clinical trials. Such advancements could revolutionize SCD management, enhancing scientific knowledge, technical capabilities, and clinical practice through the identification of novel genetic targets. These efforts have the potential to lead to groundbreaking treatments, setting new standards in the field and driving further innovation in personalized medicine.

In addition to the *HbS* variant, the severity spectrum of SCD manifests extensive clinical heterogeneity influenced by multiple genes,¹⁸ making it particularly suitable for PGx investigation. Previous genetic studies have uncovered polymorphisms that modulate different disease molecular pathways, including hemolysis, inflammation, oxidative stress, and vascular dysfunction^{18–20}. Examples include fetal hemoglobin (HbF)-regulating variants in *BCL11A* and *HBS1L-MYB*, as well as pro-inflammatory cytokine polymorphisms in *TNF-α* and *VCAM-1*, which are associated with an increased risk of stroke¹⁹. These genetic insights not only provide critical frameworks for repurposing existing drugs to target emergent SCD mechanisms but also pave the way for developing innovative, tailored therapies that could significantly improve patient outcomes²¹.

The shortage of viable treatments for SCD has prompted the exploration of alternative strategies, such as pathway-based, phenotypic, or in silico drug repurposing, leveraging existing compound libraries or approved agents to target novel SCD disease mechanisms^{22–24}. Integrating genetic data from recent high-throughput genomic studies across diverse SCD patient populations empowers the rational identification of putative druggable targets and prioritizes candidates for screening^{18,25}. However, most investigations have predominantly focused on African or African-American ancestries, with limited examination of other susceptible populations such as those in the Mediterranean and Middle Eastern regions²⁶.

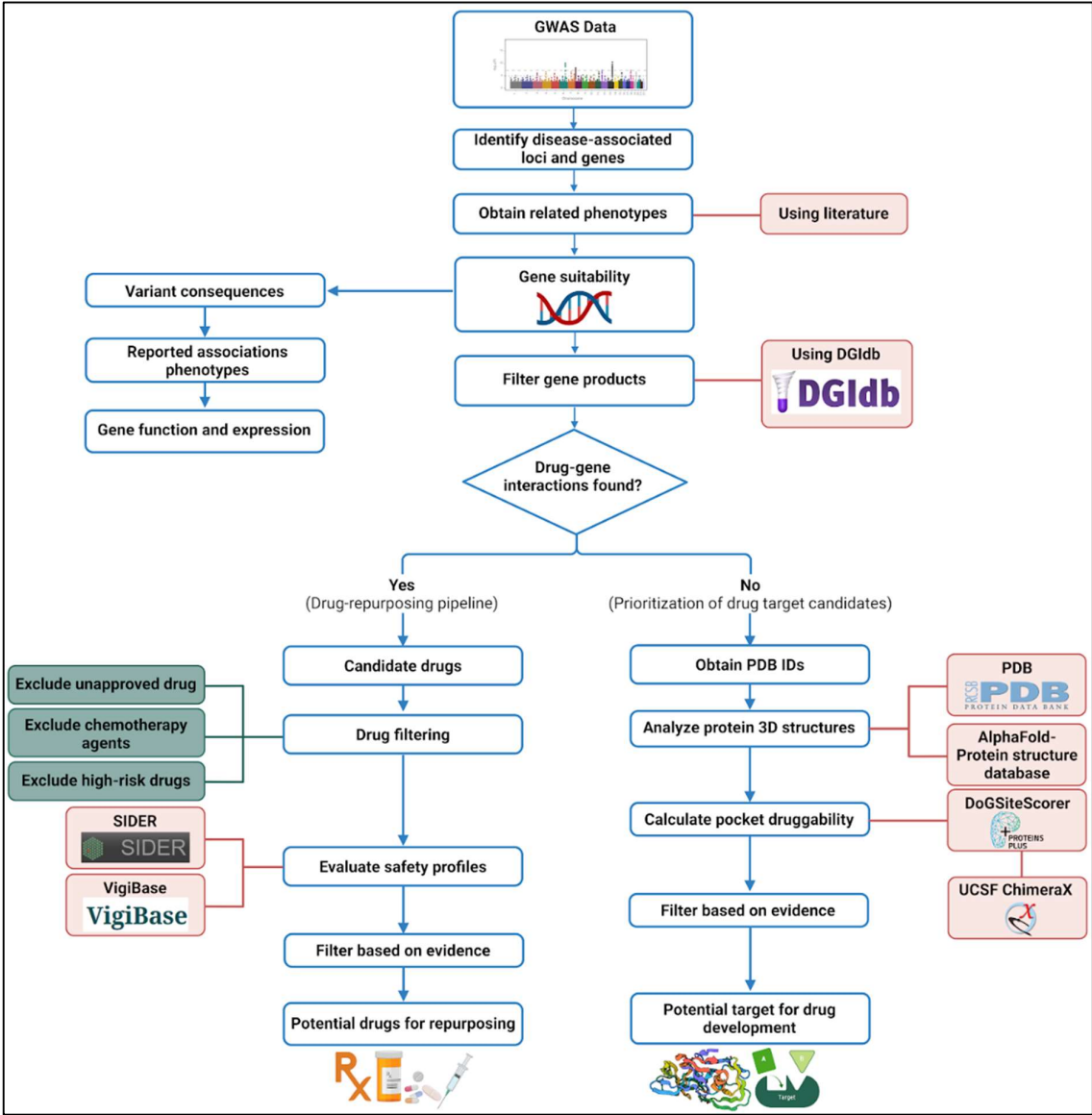
Recently, our group uncovered Saudi-enriched genetic variants that drive thromboembolic complications in SCD patients, contrasting with markers identified in other cohorts²⁵. Additionally, findings from our current data have identified several loci within known genes linked to molecular pathophysiological pathways potentially influencing SCD severity, underscoring the need for tailored interventions¹⁵. Expanding the characterization of population-specific molecular underpinnings through comprehensive genomics offers two key advantages: it uncovers novel therapeutic targets specific to Saudis and clarifies the heterogeneity in pathogenic mechanisms across the global SCD patient spectrum.

Therefore, in this study, we aimed to leverage findings from our GWAS analysis in conjunction with druggable target enrichment analysis, specifically focusing on Saudi SCD patients, to propose new SCD treatment options. Our overarching goal is to develop an informed, genetically guided roadmap that accelerates the development of innovative, population-tailored therapeutics for this historically overlooked SCD patient group. This holistic, molecular knowledge-based approach also seeks to evaluate and select the most promising druggable, non-targeted genes, thereby refining and expediting future drug discovery efforts.

2. Method

2.1. The Pipeline for Drug Repurposing and Novel Drug Development

We utilized data derived from our previous Saudi SCD GWAS analysis¹⁵ to assess the druggability of genes identified in Saudi SCD patients with potential impact on disease outcomes, aiming to establish their feasibility as therapeutic targets. Our analysis focused on identifying potential gene-drug interactions to pinpoint candidates for drug repurposing and suggesting new molecules to be developed as future treatment options. The analysis in this study followed a previously published pipeline (



)¹⁶.

2.2. Selection of SCD Severity-Associated Genes

We focused on the reported 31 genes associated with SCD severity¹⁵. These genes were selected based on their involvement in key SCD pathological pathways, including inflammation regulation, vascular function, endothelial modulation, and other disease-relevant biological processes. The selection criteria incorporated both pathway analysis of the identified genes and a comprehensive literature review, which demonstrated the functional relevance of these genes on SCD clinical phenotypes.

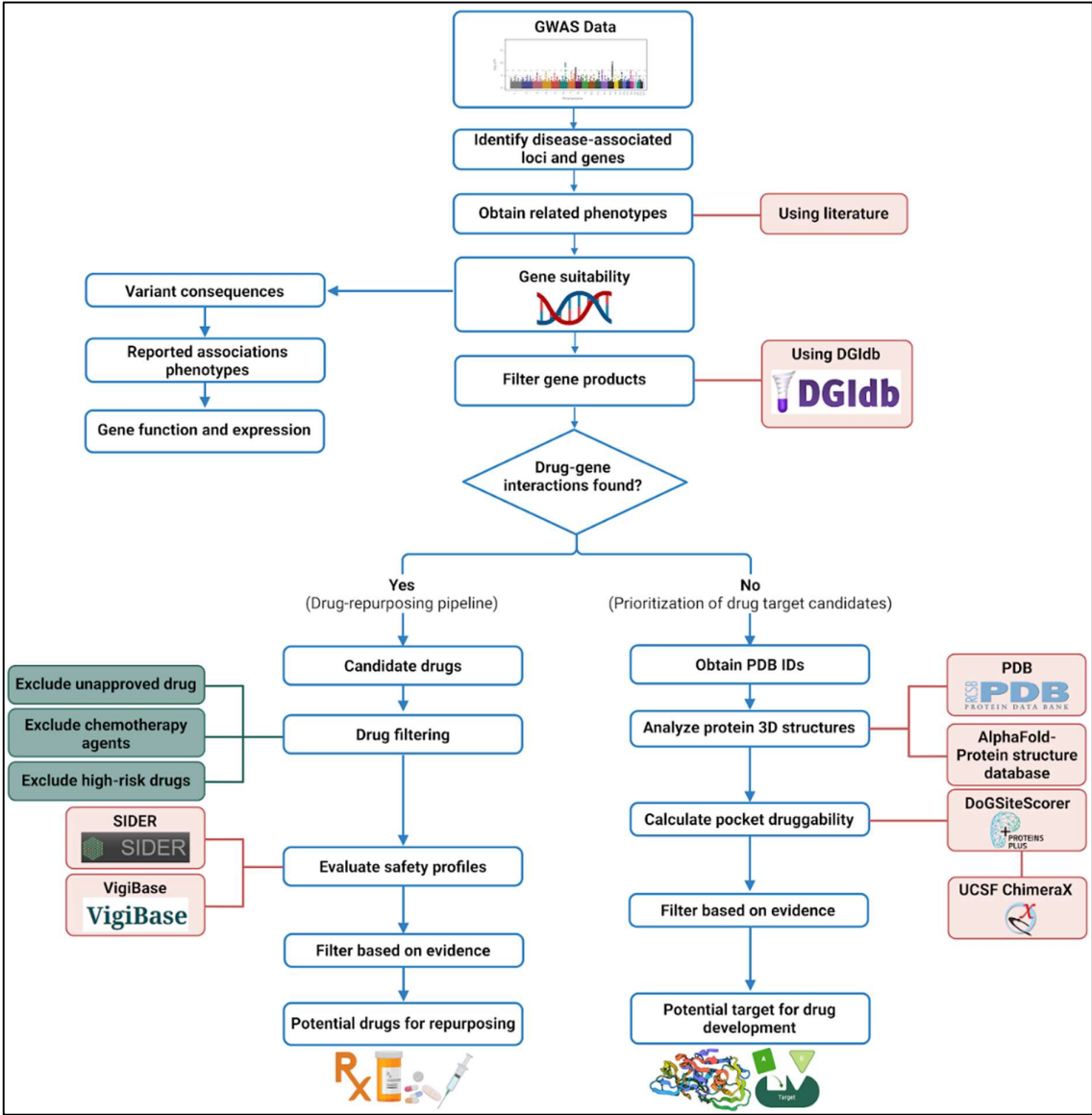


Figure 1. The Pipeline for Drug Repurposing and Novel Drug Target Identification.

2.3. Drug-Gene Interaction Analysis for Drug Repurposing

Gene products were filtered based on their potential to interact with medicinal drugs using the Drug-Gene Interaction Database (DGIdb) version 5.0, which consolidates data from multiple sources, including DrugBank and the Pharmacogenomics Knowledge Base (PharmGKB), to identify potential drug repurposing opportunities²⁷. The database provides detailed annotation of drug-gene interactions and gene druggability, covering approved drugs and **experimental compounds**.

Since gene products can interact with multiple drugs, we first excluded agents not clinically available (e.g., terminated or investigational drugs) due to their lack of immediate clinical applicability. Approved medications were then mapped to the genes of interest known impact disease pathways, excluding non-drug products.

During the initial filtration, we excluded terminated or withdrawn drugs. We prioritized medications targeting common SCD complications (e.g., inflammation, vascular dysfunction, immune dysregulation), as these pathways directly influence SCD severity. Diagnostic agents,

vitamins, supplements, and superseded medications (replaced by more effective alternatives) were also excluded.

Candidate medications were further prioritized using predicted safety profiles. Using Vigibase (the largest global adverse event repository, <https://www.vigiaccess.org/>) and the Side Effect Resource (SIDER 4.1) database (<http://sideeffects.embl.de/>), we excluded drugs linked to severe adverse reactions^{28,29}. Chemotherapy agents and drugs with serious toxicities (e.g., hepatotoxicity, cardiotoxicity) were excluded due to high-risk safety profiles. Agents posing a risk of hemolytic anemia were also removed to prevent exacerbating hemolysis in SCD patients. For comprehensive identification, we used the Search Tool for Interactions of Chemicals (STITCH) and the World Health Organization (WHO) databases to standardize drug nomenclature to match the International Nonproprietary Names (INN) and United States Adopted Names (USAN) and assign Anatomical Therapeutic Chemical (ATC) codes^{30,31}. We prioritized avoiding medications that could worsen SCD severity, especially those with risks of infection, cognitive impairment, or blood pressure instability, given SCD patients' heightened vulnerability to these complications.

2.4. Novel Drug Development Pipeline

Genes identified in our GWAS study¹⁵, with no known interaction with approved drugs, were labeled as non-targeted genes. Selection criteria included: 1) variant consequences, 2) reported associations with SCD phenotypes, 3) gene function, and 4) expression in SCD-relevant tissues. Druggability scores were calculated to assess the likelihood of a compound interacting with these gene products, based on the structural compatibility of their binding pockets with drug molecules.

Protein druggability was ranked using DoGSiteScorer³², which analyzes Protein Data Bank (PDB) structures to evaluate physicochemical interactions and identify ligand-binding pockets (<https://www.rcsb.org/>)³³. DoGSiteScorer employs a difference Gaussian filter to detect potential pockets based solely on the 3D protein structures. Score ranges between 0 and 1, with values >0.5 indicating potential druggability. This threshold was validated using 12 drug-targeted protein structures (scores: 0.68 to 0.88; Supplementary Table), enabling prioritization of candidate genes for drug development.

To address the absence of experimentally determined structures of some proteins in PDB, we used the AlphaFold database³⁴, which provides highly accurate artificial intelligence (AI)-predicted structures. AlphaFold employs deep learning to predict protein structures with near-experimentally accuracy. Notably, its developers were awarded the 2024 Nobel Prize in chemistry for this breakthrough³⁵. Combined with DoGSiteScorer, these tools enable identification of theoretical binding sites even without experimental structural data.

Predicted binding sites were visualized using UCSF ChimeraX V1.8 to generate 3D protein structure figures. Gene product expression was validated via the Human Protein Atlas (<https://www.proteinatlas.org/>)³⁶, the Gene Expression Omnibus (GEO) of the National Center for Biotechnology Information (NCBI, <https://www.ncbi.nlm.nih.gov/geo/>)³⁷, or the Genotype-Tissue Expression (GTEx) portal (<https://www.gtexportal.org/>)³⁸. Genes with predominant expression in tissues unaffected by SCD were excluded (Supplementary Table).

3. Results

3.1. Promising Candidates for Drug Repurposing

Out of the 31 genes suggested as modifiers for SCD phenotypes, 12 genes (*ACKR1*, *AGER*, *FCER1A*, *HBG2*, *HLA-A*, *HLA-DQB1*, *HLA-G*, *HLA-DRB1*, *TRIM5*, *NOTCH4*, *RRM1*, and *STIM1*) showed the ability to interact with a total of 114 distinct drug molecules. Some of these drugs (n = 36) are not yet approved for clinical use and therefore excluded. The *HBG2* gene did not show any interaction with approved drugs. Among the remaining 78 drugs, chemotherapies (n = 21), vitamins and diagnostic agents (n = 3), vaccines (n = 3), and antimicrobials (n = 12) were excluded. The remaining medications (n = 39) were further filtered based on their safety profiles.

Consequently, we excluded anticonvulsants (n = 5), antidepressants (n = 5), antithyroid (n = 3), glucocorticoids, ticlopidine, and hydralazine due to their undesirable side effects. Hydroxyurea and the analgesic agents (e.g., acetaminophen and lumiracoxib) were identified by our pipeline but were not included in the final suggested list, as they are routinely prescribed for managing SCD in clinical practice. Detection of the genes targeted by hydroxyurea (*RRM1*) and the analgesics (*HLA-DQB1*) served as benchmarks to validate the pipeline's performance (Supplementary Excel Sheet).

As a result, we narrowed down the list to the interactions between 21 medications and 6 genes, with 19 of these medications interacting with four *HLA* genes (*HLA-DQB1*, *DRB1*, *G*, and *A*). The remaining two medications (omalizumab and allopurinol) interact with two distinct genes (*FCER1A* and *NOTCH4*, respectively) (**Error! Reference source not found.**). The most frequently detected therapeutic class was the immunosuppressants (n = 12), including adalimumab, canakinumab, infliximab, omalizumab, tocilizumab, etanercept, rilonacept, peginterferon alfa-2a and 2b, azathioprine, glatiramer, and anakinra. The second most common class was lipid-modifying agents (n = 7), which included fenofibrate and statins (pitavastatin, pravastatin, atorvastatin, simvastatin, rosuvastatin, and fluvastatin).

Table 1. Predicted Drug-Gene Interactions Identified in DGI Database (V 5.0).

SNP *	Gene *	Interacting drug	ATC code (s)	Interaction Score
rs3135006	<i>HLA-DQB1</i>	Infliximab	L04AB02	0.23
		Aspirin	B01AC06/ N02BA01	0.10
		Pitavastatin	C10AA08	0.48
		Azathioprine	L04AX01	0.06
		Pravastatin	C10AA03	0.09
		Atorvastatin	C10AA05	0.04
		Simvastatin	C10AA01	0.05
		Rosuvastatin	C10AA07	0.10
		Fluvastatin	C10AA04	0.20
		Tocilizumab	L04AC07	0.48
rs2395522	<i>HLA-DRB1</i>	Adalimumab	L04AB04	0.07
		Rilonacept	L04AC04	0.80
		Canakinumab	L04AC08	1.19
		Anakinra	L04AC03	0.27
		Etanercept	L04AB01	0.09
		Infliximab	L04AB02	0.23
		Glatiramer	L03AX13	0.51
		Aspirin	B01AC06/ N02BA01	0.03
		Fenofibrate	C10AB05	0.15
		Peginterferon alfa-2a	L03AB11	0.13
rs2844806	<i>HLA-A</i>	Peginterferon alfa-2b	L03AB10	0.12
rs2524035	<i>HLA-G</i>	Simvastatin	C10AA01	1.05
rs2494250	<i>FCER1A</i>	Omalizumab	R03DX05	0.94
rs3132946	<i>NOTCH4</i>	Allopurinol	M04AA01	0.58
rs3132940				
rs9267898				
rs3096702				

* Genetic variants and mapped genes associated with sickle cell disease severity identified in our genome wide association study involving Saudi patients¹⁵.

Ultimately, we proposed immunomodulators, particularly monoclonal antibodies, and statins as potentially suitable candidates for repurposing to manage SCD severity based on their interactions with key genes that have known impact on SCD pathological pathways, as supported by literature evidence^{39,15}. Three immunomodulators working on different gene targets (omalizumab targeting

FCER1A and canakinumab and etanercept targeting *HLA-DRB1*) and a statin agent (simvastatin interacting with *HLA-G* and *HLA-DRB1*) demonstrated a high drug-gene interaction score. The antihyperuricemic agent (allopurinol), which targets *NOTCH4*, also represents a potential repurposing option.

3.2. Druggability Analysis of Non-Targeted Loci

Among the 31 genes suggested by our GWAS study¹⁵, 12 genes were shortlisted as candidates for drug repurposing, while the remaining 19 genes were assessed to identify their chemical structures and evaluate their druggability. No protein structures were detected for three gene products (*OR10J8P*, *OR10J9P*, and *HBBP1*), resulting in their exclusion. Additionally, three more genes were excluded as well: *POC5* due to an unclear role in SCD pathological mechanisms, *SCAND3* and *MMP26* due to predominant expression in irrelevant tissues (e.g., testis and endometrium).

Thirteen suitable gene targets were prioritized for drug development, with druggability scores ranging from 0.7 to 0.87. Detailed descriptions of all molecules that passed the pipeline filters are presented in **Error! Reference source not found.** The olfactory receptor (OR) gene cluster (*OR51V1*, *OR52A1*, *OR52A5*, *OR51B5*, and *OR51S1*) and the Tripartite Motif gene family (*TRIM6*, *TRIM22*, and *TRIM34*) emerged as prominent candidates. More details about all screened molecules are available in Supplementary Table. The OR gene cluster, particularly *OR51V1*, *OR51A1*, and *OR51B5*, has been extensively linked to SCD phenotypes in the literature. Additionally, *TRIM6*, *SIDT2*, and *CADM3* were suggested due to their high expression in SCD-related tissues and their potential roles in the related complications. These promising protein candidates, along with their structural visualizations and druggability scores, are shown in

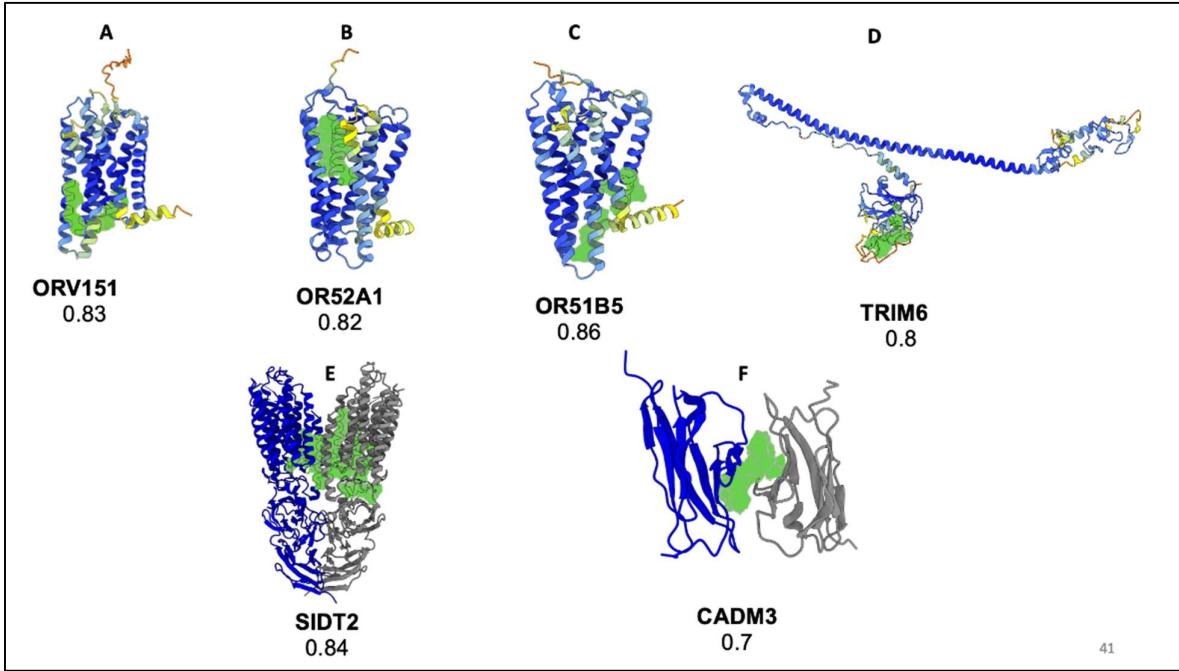


Figure 1.

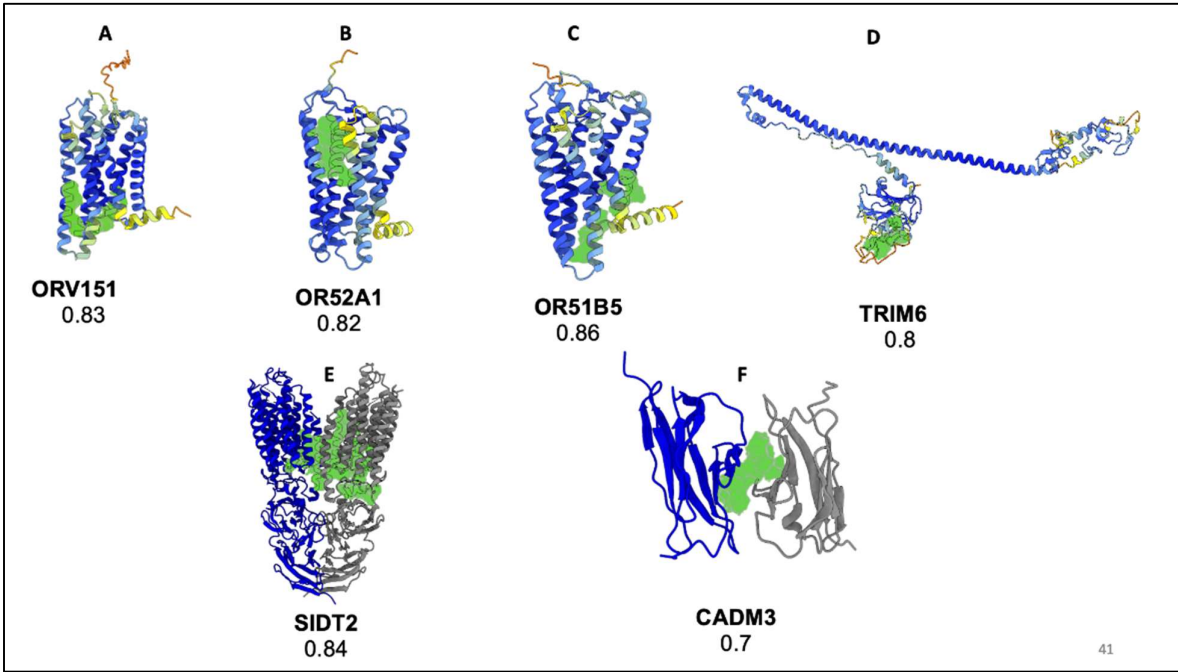


Figure 1: Three-dimensional structural representations of selected proposed proteins. Legend: A) *OR51V1*, B) *OR52A1*, C) *OR51B5*, D) *TRIM6*, E) *SIRT2*, and F) *CADM3*. The predicted optimal druggable binding site for each protein is highlighted in green.

Table 2. Most Suitable Drug Targets Based on Predicted Pocket Interactions Utilizing DogSiteScorer Database.

SNP	Gene	Pocket Score	PDB Code	AlphaFold Code
rs7933549	<i>OR51V1</i>	0.83	----	AF-Q9H2C8-F1
rs112098990	<i>OR52A1</i>	0.82	----	AF-Q9UKL2-F1
rs2472530	<i>OR52A5</i>	0.82	----	AF-Q9H2C5-F1
rs147062602	<i>OR51B5</i>	0.86	----	AF-Q9H339-F1
rs10838058				
rs10837853				
rs78253695				
rs180750244				
rs12361955	<i>OR51S1</i>	0.84	----	AF-Q8NGJ8-F1
rs3740999	<i>TRIM6</i>	0.8	----	AF-Q9C030-F1
rs11038294				
rs12272467				
rs67573252	<i>TRIM22</i>	0.87	----	AF-Q8IYM9-F1
rs2342380	<i>TRIM34</i>	0.82	2EGP	----
rs10535646	<i>SIRT2</i>	0.84	7Y68	----
rs3845624	<i>CADM3</i>	0.7	1Z9M	----
	<i>MPTX1</i>	0.81	----	AF-A8MV57-F1

* Genetic variants and mapped genes associated with sickle cell disease severity identified in our genome wide association study involving Saudi patients¹⁵.

4. Discussion

Applying genetics knowledge to enable the repurposing of drugs has emerged as a promising and innovative strategy in the field of pharmacology. In 2021, the U.S. Food and Drug Administration (FDA) approved approximately two-thirds of new medications based on genetic insights^{40,41}. The

development and application of advanced genetic analysis approaches such as GWAS and next-generation sequencing (NGS) [e.g., whole-genome sequencing (WGS) and whole-exome sequencing (WES)] have significantly deepened our understanding of the genetic underpinnings of complex traits^{42,43}. This progress facilitated the identification of promising drug targets through the discovery of causative genetic variants⁴⁴. However, effectively translating these genetic discoveries into clinical practice remains challenging, particularly for conditions like SCD with diverse phenotypes influenced by multifactorial genetic associations. The use of already authorized medications for new applications at more affordable costs is increasingly recognized as a valuable and expanding approach^{16,40,45}. Several previous studies have utilized in silico pipeline to suggest potential drug candidates and identify target molecules for treating various medical conditions by leveraging findings from publicly available GWAS analyses^{16,46,47}. Different GWAS databases are available and can be used to understand the genetic basis of selected diseases. Therefore, it is possible to translate identified signals into therapeutic targets using genomic-based approaches and a well-established pipeline¹⁶. In our project, we adopted a similar methodology to propose novel drug treatment options that could potentially target specific genes known to impact outcomes in SCD patients.

In a previous GWAS study, we identified multiple genes that play a significant role in SCD and its complications¹⁵. Furthermore, the current study aimed to maximize the utility of existing data to translate genetic knowledge into clinical care of SCD. Thus, 21 approved agents were identified as having strong affinity to interact with the reported genes modulating various SCD phenotypes. The chosen drug candidates are classified into lipid-modifying and immunomodulatory agents, with the potential to modulate multiple pathways in SCD, including sickling, hemolysis, and inflammation⁴⁸. Based on unique criteria, the filtering process highlighted five highly promising candidates for repurposing: simvastatin, allopurinol, canakinumab, omalizumab, and etanercept.

In addition to simvastatin, other statins were also identified—such as atorvastatin, pravastatin, fluvastatin, rosuvastatin, and pitavastatin—have also shown promise for SCD management due to their anti-inflammatory properties. These agents downregulate the transcription factor NF- κ B, inhibit the expression of key pro-inflammatory cytokines such as TNF and IL1B, and enhance endothelial function by restoring nitric oxide (NO) bioavailability and reducing the expression of adhesion molecule, collectively contributing to the vascular protective effects^{49,50}. Notably, the JUPITER trial, a key intervention study evaluating rosuvastatin, demonstrated the immunomodulatory potential of statins, with rosuvastatin significantly reducing C-reactive protein (CRP) levels by approximately 37%, further supporting the role of statins in mitigating inflammation-related complications⁵¹.

Simvastatin was suggested as the optimal candidate among all statins due to its superior interaction score and clinical relevance. While other statins interact with the *HLA-DRB1* only, which encodes a major histocompatibility complex protein, simvastatin uniquely interacts with both *HLA-DRB1* and *HLA-G*. These proteins are integral to immune responses that exacerbate SCD complications, such as vaso-occlusive crises and organ damage^{52–55}. Furthermore, simvastatin has shown a greater capacity to reduce von Willebrand factor (vWF) levels, underscoring its crucial role in managing SCD-associated hypercoagulability^{56,57}.

A clinical study in a small SCD cohort ($n = 26$) demonstrated that short-term simvastatin administration significantly improved nitric oxide bioavailability by approximately 52% ($p = 0.01$) and suppressed systemic inflammatory biomarkers such as CRP and IL-6, both of which are associated with increased vascular dysfunction risks in SCD⁵⁸. Moreover, a pilot study on 19 SCD patients reported that simvastatin reduced the occurrence of vaso-occlusive pain by 85% ($p = 0.0003$) and decreased the use of analgesics by 67% ($p = 0.003$). It also showed a significant reduction in circulating CRP, soluble (s) E-selectin, intercellular adhesion molecule 1 (sICAM-1), sICAM-3, and vascular endothelial growth factor, with the most pronounced effects observed in patients concurrently receiving hydroxyurea⁵⁹.

In vitro studies further underscore simvastatin's potential, showing a 1.9-fold increase in fetal hemoglobin expression and a 30–35% reduction in irreversibly sickled cells under hypoxic

conditions⁶⁰. An ongoing clinical trial is currently assessing simvastatin's effects on central nervous system vasculature in SCD patients (ClinicalTrials.gov Identifier: NCT03599609)¹⁰. Based on this robust body of evidence and specific criteria, we recommend simvastatin as the ideal drug for repurposing in SCD, although other statins may also offer benefits depending on individual patient factors. Further research, including large randomized controlled trials, is warranted to fully elucidate simvastatin's therapeutic potential in this context.

Another suggested repurposing candidate is allopurinol, which targets products of the *NOTCH4* gene. This gene is a member of the *NOTCH* family, well known for its role in regulating endothelial function and exerting anti-inflammatory effects, as well as influencing hematopoiesis, all of which may contribute to alleviating disease severity^{61,62}. In the Saudi SCD dataset, we identified the marker rs3132946 in *NOTCH4*, which has been previously reported as a marker linked to interstitial lung diseases (ILD)⁶³. This condition is notably common in SCD patients, with 74% of adults in a large prospective cohort study exhibiting a restrictive pattern on pulmonary function tests⁶⁴. While not all adults with SCD show the common features of sickle cell lung disease (SCLD), this restrictive pattern remains the most consistent clinical manifestation, underscoring its significant impact on this population.

Allopurinol, a well-established xanthine oxidase inhibitor long used to treat hyperuricemia in patients with gout or tumor lysis syndrome⁶⁵, has demonstrated broader vascular benefits. It can protect vascular tissue from oxidative stress and repetitive reperfusion injury, both of which are critical components of SCD pathology⁶⁶. By inhibiting the production of reactive oxygen species (ROS), allopurinol preserves nitric oxide availability, thereby supporting vascular relaxation and function⁶⁷. Preclinical studies in sickle cell models show mixed results; while one study reports no significant effect on cell adhesion, another showed improved blood flow and reduced leukocyte recruitment upon exposure to allopurinol^{68,69}. Given the oxidative stress and endothelial dysfunction observed in SCD, further exploration of allopurinol's therapeutic potential, particularly in combination with other agents, is warranted. However, careful consideration of its side effects, including hypersensitivity and rare severe reactions, is crucial. Even in populations where the *HLA-B*5801* allele is not highly prevalent, such as the Saudi population⁷⁰, it is still important to genotype for *HLA-B*5801* to mitigate the risk of hypersensitivity reactions when prescribing allopurinol⁷¹.

Omalizumab was initially approved in 2003 by the US FDA for the treatment of moderate to severe persistent asthma, with expanded indications in subsequent years⁷². This medication, which targets the *FCER1A* gene product, has emerged as one of the top candidate repurposing drugs. This recombinant immunoglobulin G (IgG) is a monoclonal antibody that selectively binds to free IgE, thereby attenuating allergic asthma. By preventing IgE from interacting with high-affinity Fcε receptors on effector cells such as mast cells, omalizumab modulates downstream pro-inflammatory signaling that leads to airway inflammation and may also potentially reduce coagulation abnormalities associated with disease activity⁷³.

In the Saudi SCD cohort, the marker rs2494250 in the *FCER1A* was detected. This variant was previously reported as significantly associated with elevated levels of inflammatory biomarkers, including CCL2/MCP-1⁷⁴. Furthermore, studies have reported a higher prevalence of IgE among Saudis with SCD, potentially increasing the risk of acute chest syndrome (ACS). Notably, ACS accounts for 25% of ICU admissions and 28.5% of deaths among SCD patients, with particularly high rates observed in individuals from Al-Hasa region^{75–77}. Thus, further clinical studies in SCD patients are warranted to confirm omalizumab benefits in mitigating this disease complication.

Our pipeline has also identified other biological disease-modifying drugs targeting the *HLA-DRB1* gene. Canakinumab and etanercept were suggested as favorable candidates for repurposing in SCD management. Canakinumab can selectively target IL-1β, a cytokine with a central role in the inflammatory process, and may contribute to modulating disease pathways in SCD^{10,78}.

Moreover, canakinumab has been studied on 74 children and young adults with SCD in a recent double-blind, randomized study^{10,79}. It demonstrated a tolerable safety profile, in contrast to other monoclonal antibodies that are often associated with a high risk of infection^{80,81}. Although this clinical

study did not achieve its primary goal of reducing daily pain compared to baseline, it showed several beneficial effects, including lower levels of inflammatory biomarkers, reduced hospitalization rates, and improvements in patient-reported outcomes such as fatigue and absenteeism from school or work^{79,82}. Additionally, there is an ongoing clinical study evaluating its safety in pediatric SCD patients (ClinicalTrials.gov Identifier: NCT02961218)¹⁰. Consequently, further clinical studies involving a larger number of patients are warranted to confirm canakinumab's role in reducing inflammation and improving disease outcomes in Saudi SCD patients.

On the other hand, etanercept, a TNF- α receptor blocking agent, may halt inflammatory signaling initiated by TNF- α . Episodes of ischemia-reperfusion injury that commonly lead to vascular dysfunction and subsequent vaso-occlusion in SCD, may be minimized with etanercept therapy²⁴. Long-term exposure of mice with SCD to etanercept resulted in a reduction of acute disease manifestations, including vaso-occlusion, responses to pain stimuli, leukocytes, and inflammatory biomarkers⁸³. In addition, two case reports of patients with rheumatoid arthritis and SCD were treated successfully and safely with etanercept⁸⁴. This encouraging evidence supports the need for conducting clinical trials to assess etanercept's outcomes in SCD patients.

These suggested agents show promising potential in managing SCD severity and offer diverse features, including different routes of administration and cost advantages, which could facilitate their clinical adoption. For instance, simvastatin and allopurinol are widely used, available as oral formulations, and offered as affordable generics, which enhances their accessibility for long-term use^{85,86}. In contrast, monoclonal antibodies also impact disease severity pathways; however, they require subcutaneous injections, often administered during hospital visits every 4–8 weeks, making them less convenient. Additionally, their higher costs compared to oral medications may limit accessibility^{87,88}. Thus, oral agents offer greater convenience as they can be taken at home daily, potentially improving adherence, especially in chronic conditions like SCD. While injectable biologics may be more potent, they present challenges related to frequent healthcare interactions, administration, and higher costs. Strategically selecting these medications based on patient compliance and healthcare setting considerations may provide valuable therapeutic options for managing SCD complications.

The complex pathophysiology of SCD necessitates targeting multiple possible disease mechanisms. Thus, a multi-drug approach is suggested to address factors such as fetal hemoglobin modulation, cell adhesions and sickling, inflammation, ischemia/reperfusion, oxidative stress, coagulation, and free heme toxicity. To achieve this, a combination of drug therapies with different mechanisms is warranted²⁴.

In exploring new potential drug targets, we successfully identified the druggability pocket in several previously non-targeted gene products within this pipeline. We strongly recommend *OR* gene clusters as novel targets, particularly *OR51V1*, *OR52A1*, and *OR51B5*. Important mutations in these genes—such as rs7933549 (missense), rs112098990 (frameshift), and rs147062602 (frameshift), respectively—are commonly carried by SCD individuals and are associated with defects in protein function and subsequent degradation. As shown in the GTEx portal, this gene cluster is notably expressed in whole blood and erythroid cells near the β -globin cluster, which plays a regulatory role in hemoglobinopathies^{89–91}. Although these are pseudogenes—non-functional DNA segments that do not directly contribute to phenotypic traits—they may regulate gene expression and function. Numerous genetic variants mapped to these gene products have been reported in the literature with multiple SCD phenotypes from previous GWAS and large meta-analyses, providing strong evidence of *OR* genes involvement in hematological parameters and SCD complications^{18,25}. The reported traits associated with various mutations in the *OR* genes include level measurements of hemoglobin, hematocrit, erythrocyte count, mean corpuscular volume, red blood cell distribution width, mean corpuscular hemoglobin concentration, mean reticulocyte volume, fetal hemoglobin level, leukocyte count, monocytes, neutrophils, CRP, and platelet levels. Clinical complications such as hemolysis, thromboembolism, ischemia, and cardiomyopathy in SCD have also been previously linked to these genes^{90–92}.

The pipeline also suggests *TRIM 6*, *SIDT2*, and *CADMD3* as novel, promising therapeutic targets. TRIM family proteins, including TRIM6, TRIM22, and TRIM34, are involved in innate immune modulation, cell cycle progression, and transcriptional regulation, suggesting they may influence inflammation, oxidative stress, hematopoietic stem cell differentiation, and immune responses⁹³. These processes are critical to SCD pathophysiology and its complications. Furthermore, the *SIDT2* gene product may contribute to SCD-related outcomes, as its dysregulation is linked to several metabolic traits associated with hepatic disorders, cardiovascular dysfunctions, and SCD-nephropathy^{94,95}. Meanwhile, *CADM3*, which is involved in cell cycle regulation and epithelial proliferation⁹⁶, may impact hematological traits, thereby affecting blood cell formation and function in SCD. Each of these targets has a high druggable score, ranging from 0.7 to 0.86, highlighting them as strong candidates for future drug development.

3.5. Limitation

While the current study presents a promising framework to repurpose approved drugs as well as identify new drug targets for managing SCD severity, several limitations should be considered. First, our approach relies in part on in silico predictions and bioinformatic analyses, which, while powerful, cannot fully capture the complexities of drug-target interactions in vivo. This was partially addressed by the availability of various animal and small clinical trials that support our findings, yet larger, prospective clinical trials remain necessary. Additionally, the druggability scores that were used to prioritize the candidate targets for discovering new drug molecules were derived from computational models, which may not accurately reflect true biological conditions. Furthermore, the absence of direct clinical evidence concerning some of the proposed targets, such as *SIDT2* and *CADM3*, in relation to SCD outcomes underscores the need for further experimental validation.

3.6. Conclusions

Utilizing an established pipeline enabled us to identify several promising candidates for drug repurposing, notably statins, immunomodulatory agents, and allopurinol. Additionally, novel targets—specifically *OR* and *TRIM* gene families—were identified for potential drug development to mitigate SCD severity and complications, with a focus on the Saudi population. The selection of these gene targets was supported by high pocket druggability scores and their involvement in key molecular pathways underlying the disease. These findings not only enhance our understanding of the genetic basis of SCD but also pave the way for more targeted and effective therapeutic approaches. Future clinical trials are essential to validate these computational predictions and translate them into actionable therapies that can improve outcomes for SCD patients.

Institutional Review Board Statement: The study received ethical approvals from the Institutional Review Boards (IRBs) of King Abdullah International Medical Research Center (KAIMRC), Saudi Arabia (Ref: IRBC/1414/19), and Virginia Commonwealth University (VCU), the United States of America (HM20030698). No informed consent was required for this study, as only publicly available data were used and no individual-level or identifiable information was accessed.

Authors' contribution: **AA:** Conceptualization, Methodology, Data curation, Software, Formal analysis, Writing – original draft; **MAA:** Supervision, Project administration, Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing; **DW:** Validation, Writing – review & editing; **MA:** Data curation, Resources, Writing – review & editing; **SA:** Investigation, Resources, Writing – review & editing; **KA:** Data curation, Software, Writing – review & editing; **MK:** Resources, Validation, Writing – review & editing; **ASA:** Supervision, Funding acquisition, Writing – review & editing; **II:** Conceptualization, Supervision, Writing – review & editing.

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