



A Systematic Review and Meta-Analysis of HLA-DR in Onychomycosis: HLA-DR8 Confers Susceptibility

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Introduction

- Onychomycosis represents about half of most toenail health concerns of patients worldwide.
- Dermatophytes, yeasts, and non-dermatophyte molds have been implicated as causal agents. Among dermatophytes, *Trichophyton rubrum* is the most prevalent, responsible for 90% of cases in North America.
- Certain underlying health conditions, environmental influences, and genetic predispositions play a role in developing the condition.
- HLA-DR is a component of the major histocompatibility complex class II, a highly polymorphic genomic region that plays a crucial role in the immune system by encoding molecules involved in antigen presentation.
- While many individual studies have examined the role of HLA-DR in onychomycosis, none have analyzed them together to determine if there is a significant effect on onychomycosis susceptibility.

Study Objective

- Perform a systematic review and meta-analysis to evaluate HLA-DR allele involvement in onychomycosis susceptibility.

Methodology

- Preferred Reporting Items for Systematic Reviews & Meta-Analyses (PRISMA) guidelines were followed (Figure 1).
- The following search terms were input into each of the databases: "HLA Onychomycosis", "Genetic Susceptibility to Onychomycosis" and "HLA-DR Onychomycosis".
- Studies that contained HLA-DR allele frequency data on patients with onychomycosis were included. Studies that contained HLA-DR alleles with too high resolution, did not provide allele frequency or odds ratio data, did not provide HLA-DR data, written in a non-English language, or used animals as subjects were excluded.
- From these articles, allele frequency data, 95% CI's, and population characteristics such as ethnicity, study methods, fungal species, and study design were collected (Table 1).

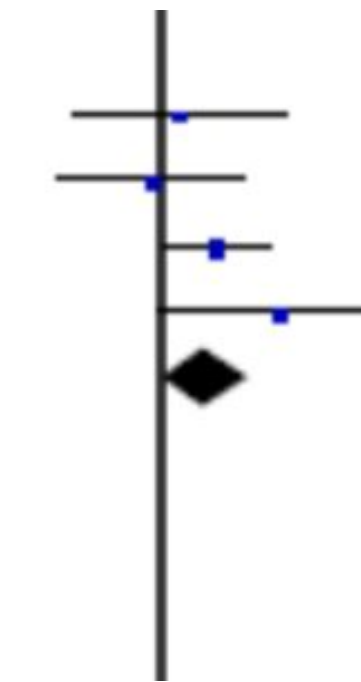
Results

1.1.7 HLA-DR8

Author(s)	Year	Cases	Controls	Total	OR	95% CI	Year	
Svejgaard et al., 1982 [28]	1982	3	28	61	704	2.0%	1.26 [0.37, 4.31]	1982
Asz-Sigall et al., 2010 [19]	2010	6	42	13	84	2.7%	0.91 [0.32, 2.59]	2010
Garcia-Romero et al., 2012 [20]	2012	15	71	93	762	6.5%	1.93 [1.05, 3.55]	2012
Carillo-Melendrez et al., 2016 [29]	2016	12	50	3	40	1.7%	3.89 [1.02, 14.93]	2016
Subtotal (95% CI)			191	1590	12.8%	1.70 [1.05, 2.76]		

Total events: 36 / 170
 Heterogeneity: Tau² = 0.02; Chi² = 3.21, df = 3 (P = 0.36); I² = 7%
 Test for overall effect: Z = 2.15 (P = 0.03)

Figure 2 – HLA-DR8 Forest Plot



The association between HLA-DR markers and the incidence of onychomycosis was analyzed across five studies published between 1982 and 2016.

The analysis includes data on individual studies and their pooled results, providing odds ratios (ORs) and 95% confidence intervals (CIs) for the association between different HLA-DR markers and onychomycosis.

The pooled odds ratios for HLA-DR markers 1-7 and 9-16 did not show a statistically significant association with onychomycosis, as their confidence intervals included 1.

HLA-DR8 showed a statistically significant association with onychomycosis, with an OR of 1.70; 95% CI [1.05-2.76] (Figure 2).

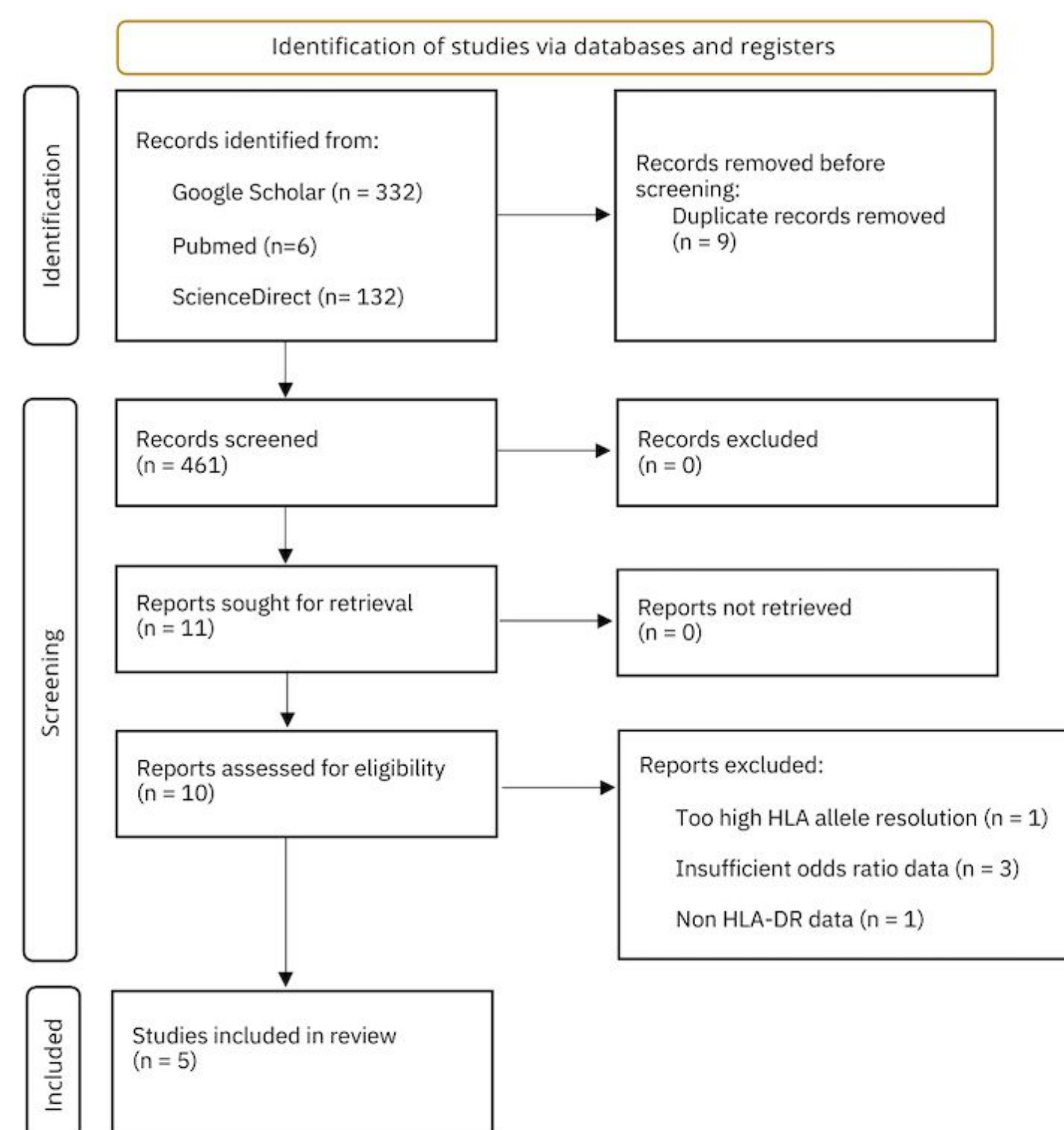


Figure 1 – PRISMA Flow Diagram

Author(s)	Year	Sample Size	Population	Study Design	Study Methods	Infectious Agent	HLA variants studied	Main Findings
Svejgaard et al. [28]	1982	34 cases 58-704 controls	Unspecified	Prospective case-control	Tissue typing using the 7th workshop technique for DR antigens Fungal ID method not stated	<i>T. rubrum</i>	HLA-DR 1-5, 7-10	HLA-DR does not significantly affect susceptibility to onychomycosis.
Ahmed et al. [27]	1985	29 cases 558 controls	Caucasian Mean age = 54	Prospective case-control	Fisher's exact test Cytotoxicity test KOH Microscopy Woolfe method (relative risk)	Unspecified	HLA-DR 1-7	In the presence of a personal or family history of atopy, HLA-DR4 demonstrates an association with onychomycosis.
Asz-Sigall et al. [19]	2010	21 cases 42 controls	Mexican-Mestizo Mean age = 40	Prospective case-control	HLA typing via PCR sequence-specific primer-based assay Direct microscopy and culture SPSS/PC v14.0 and EGRET (odds ratio)	<i>T. rubrum</i>	HLA-DR 1-8	HLA-DR6 confers protection against onychomycosis.
Garcia-Romero et al. [20]	2012	47 cases 31 controls	Mexican-Mestizo Mean age unspecified	Prospective case-control	HLA typing via PCR sequence-specific primer-based assay Direct microscopy or culture StatCalc program in Epi (odds ratio)	Unspecified	HLA-DR 1, 3, 4, 7, 8, 10-16	HLA-DR8 increases susceptibility to onychomycosis.
Carillo-Melendrez et al. [29]	2016	25 cases 20 controls	Mexican-Mestizo Mean age = 50	Prospective case-control	HLA typing via PCR sequence-specific primer-based assay KOH direct microscopy and Sabouraud dextrose agar and BBL Mycosel agar culture StatCalc program in Epi (odds ratio)	Unspecified	HLA-DR 1, 3, 4, 7, 8, 11, 13-16	Both HLA-DR8 and -DR1 are associated with increased susceptibility to onychomycosis.

Table 1 – Study Characteristics

Discussion

Clinical Importance

These new insights may help identify at-risk populations as well as inform the development of future prophylactic and therapeutic interventions. Individuals identified as genetically predisposed should be advised to avoid environmental factors such as sweating and occlusive footwear, as these factors have been shown to increase risk. Disease-associated genes may affect response to pharmacologic treatment. By tailoring therapy to an individual's specific genetic profile, it may be possible to enhance clinical outcomes and improve the overall management of onychomycosis.

Limitations & Future Studies

Many studies concentrate on specific populations such as the Mexican Mestizo group. Therefore, larger cohorts with more diverse patient populations should be studied to improve the generalizability of the findings. Additional variables such as environmental factors, other genetic variations, and pre-existing conditions may also influence susceptibility and potentially confound the results. Investigating gene-environment and polygenic influences would offer a more comprehensive understanding of these very complex interactions.

Conclusions

Our findings indicate a potential relationship between HLA markers and the risk of developing onychomycosis, with the HLA-DR8 allele appearing to increase susceptibility. However, additional research is required to fully elucidate and expand upon this relationship.

References

